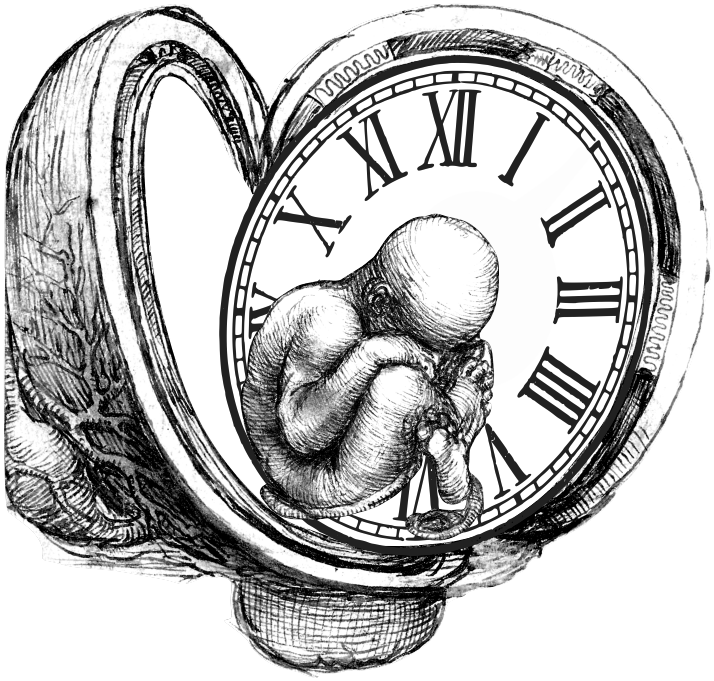
Waking up early

The effect of premature birth on chronotype, sleep, and health-related quality of life



JOHAN BJÖRKQVIST
University of Helsinki

Waking up early

The effect of premature birth on chronotype, sleep, and health-related quality of life

Johan Björkqvist

Doctoral Programme in Clinical Research,
Doctoral School in Health Sciences
Faculty of Medicine,
University of Helsinki, Finland

Children's Hospital and Pediatric Research Center
Helsinki University Hospital and
University of Helsinki, Finland

Finnish Institute for Health and Welfare,
Finland

DOCTORAL DISSERTATION

To be presented for public discussion,
with the permission of the Faculty of Medicine of the University of Helsinki,
in Lecture Hall 2 of the Haartman Institute, Helsinki,
on the 10th of January 2020 at 12 noon.

Helsinki 2020

Cover illustration and its derivative by the author, modified from Leonardo Davinci's *Studies of the Fetus in the Womb* c. 1511 (public domain image), retrieved from https://en.wikipedia.org/wiki/Studies_of_the_Fetus_in_the_Womb, 21.12.2017.

ISBN 978-951-51-5662-4 (paperback)

ISBN 978-951-51-5663-1 (online)

http://ethesis.helsinki.fi

Hansaprint, Vantaa, Finland

2020

Supervisors

Professor **Eero Kajantie**

Public Health Promotion Unit,
Finnish Institute for Health and Welfare,
Finland

PEDEGO Research Unit,
University of Oulu,
Finland

Department of Clinical and Molecular Medicine,
Norwegian University of Science and Technology,
Norway

Professor **Anu-Katriina Pesonen**

SleepWell Research Program,
Faculty of Medicine,
University of Helsinki,
Finland

Docent **Petteri Hovi**

Public Health Promotion Unit,
Finnish Institute for Health and Welfare,
Finland

Pre-examiners

Docent **Christian Benedict**

Sleep Research Laboratory,
Department of Neuroscience,
Uppsala University,
Sweden

Docent **Päivi Korhonen**

Department of Paediatrics,
Tampere University Hospital,
Finland

Tampere Center for Child Health Research,
Tampere University Hospital and University of Tampere,
Finland

Opponent

Professor **Susan Redline**

Peter C. Farrell Professor of Sleep Medicine,
Harvard Medical School,
USA

Division of Sleep and Circadian Disorders,
Departments of Medicine and Neurology,
Brigham and Women's Hospital,
USA

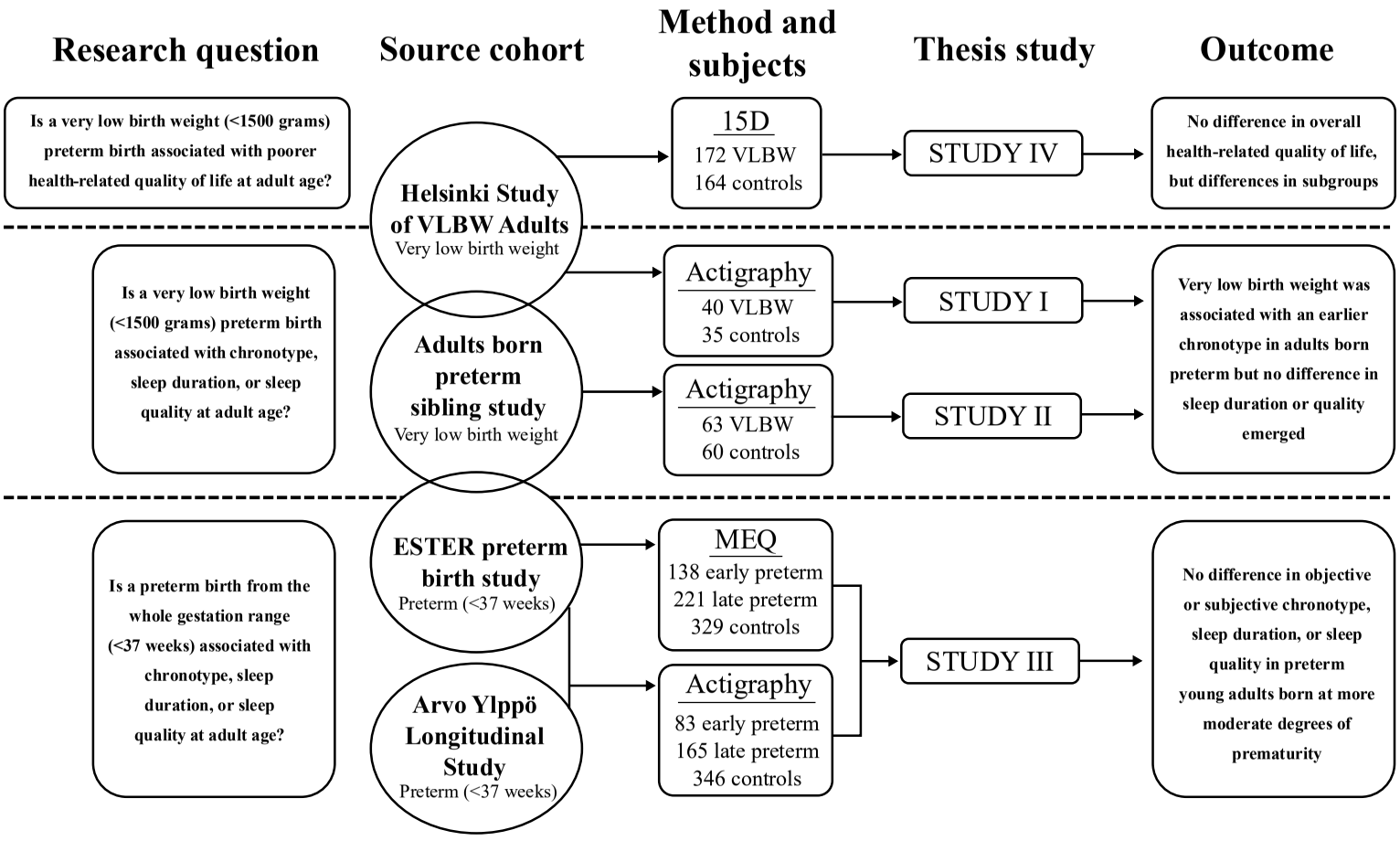
Division of Pulmonary Medicine,
Department of Medicine,
Beth Israel Deaconess Medical Center,
USA

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations

“The same biological clock ticks away in humans and fruit flies, which underscores the importance of circadian timing to life on this planet.”

Excerpt from the Nobel banquet speech by Michael Rosbash, who together with Jeffrey C. Hall and Michael W. Young received the 2017 Nobel Prize in Physiology or Medicine.

THESIS AT A GLANCE



Abstract

Background. Premature birth can be a harsh start to life; globally it is the leading cause of death in children under five and the outlook is grimmer the smaller the child. This perilous beginning is not the only adversity these survivors face, however. Decades-long follow-up studies have revealed subtle impairments in many domains of mental and physical health, intellectual achievement, and wellbeing, especially in survivors born preterm (<37 weeks gestation) with a very low birth weight (VLBW, <1500 g). These studies have described many long-term outcomes in detail, but other important subjects, such as sleep and chronotype have received far less attention. Chronotype is the personal preference for the timing of activity and sleep; it is a behavioural manifestation of the internal circadian clock, and people with very early or late preferences are sometimes called morning larks and night owls. Chronotype, sleep duration, and sleep quality are all important and independent predictors of health and wellbeing, and interestingly, studies have shown that late chronotype and poor sleep are associated with similar adversities as prematurity, such as poorer mental and cardiometabolic health. This raises the question if late chronotype, poor sleep, and prematurity are associated. Novel studies of prematurity-related morbidity expand our knowledge of the phenomenon, but some fundamental questions also require regular revisiting, such as: do survivors of early modern neonatal care have poorer quality of life?

Aim. This thesis investigated if preterm birth and VLBW are associated with adult chronotype, sleep duration, sleep quality, or health-related quality of life (HRQoL).

Methods. This thesis investigated adult preterm subjects and term-born controls from four different but in part overlapping studies and birth cohorts: The preterm subjects of The Helsinki Study of VLBW Adults (HeSVA) received treatment in the neonatal intensive care unit (NICU) of the Children's Hospital in 1978-85. The subjects of the ESTER Preterm Birth Study came from the Northern Finland Birth Cohort 1986, and a cohort of subjects born 1987–89 in the same area, identified via the Finnish Medical Birth Register (FMBR). The Arvo Ylppö Longitudinal Study (AYLS) is part of a multicentre follow-up study of subjects admitted to neonatal wards or the Children's Hospital NICU in 1985-86. The preterm subjects of ESTER and AYLS are from the whole gestation range, classified as early preterm (<34 weeks) and late preterm (34 to <37 weeks). The Sibling Study consists of VLBW adults and their term-born siblings. The preterm subjects consisted of previous participants from the HeSVA (1978-85) and ESTER

(1987-89) studies, and new recruits identified via the FMBR, born in 1987-90 in the University Hospitals of Turku or Tampere, or in the hospital district of Helsinki-Uusimaa.

This thesis used wrist-worn accelerometers called actigraphs to objectively measure sleep timing, duration, and quality. The main measure for chronotype was sleep midpoint on free days corrected for sleep debt, MSFsc. Further, this thesis utilized the Morningness-Eveningness Questionnaire to investigate subjective chronotype, and the 15D instrument to provide information about HRQoL.

Results. Study I compared actigraphy data of 40 VLBW young adults and 35 controls in the HeSVA cohort at a mean age of 25.0 years (SD 2.2). It discovered that preterm participants displayed a significantly earlier corrected sleep midpoint (65 min, 95% CI 14 to 116 min, $p = 0.013$) than term-born controls. No difference in sleep duration or quality emerged.

Study II compared actigraphy data of 63 VLBW subjects and 60 term-born siblings (53 complete pairs) at a mean age of 29.8 years (SD 4.1). The corrected sleep midpoint was again earlier in the VLBW group (46 min, 95% CI 16 to 77 min, $p = 0.004$), and again neither sleep duration nor quality differed meaningfully.

Study III compared actigraphy data of 83 early and 165 late preterm subjects to 346 term-born controls in the pooled ESTER-AYLS cohort (mean age 24.3, SD 1.3). No difference in corrected sleep midpoint, sleep duration, or sleep quality emerged. Further, the Morningness-Eveningness Questionnaire was completed by 138 early preterm, 221 late preterm, and 329 control subjects in the ESTER study: neither the distribution of chronotype nor the Morningness-Eveningness Score differed between groups.

Study IV compared the health-related quality of life of 164 VLBW and 172 control subjects in the HeSVA cohort at a mean age of 22.5 years (SD 2.1). Overall the preterm group reported similar HRQoL to controls, but subgroup analysis revealed differences. VLBW adults born small for gestational age (SGA) reported worse HRQoL (0.911 versus 0.939, $p = 0.039$) than VLBW adults born appropriate for gestational age (AGA), possibly because AGA-VLBW men scored well, whereas VLBW women born SGA scored worse HRQoL.

Conclusion. Contrary to expectations, preterm subjects displayed an *earlier* chronotype rather than later. This finding was limited to those born smallest; comparison of less preterm groups to controls did not discover any discernible differences. Sleep duration

and quality do not seem to differ from controls, nor does the health-related quality of life in general, even if subgroups showed clear differences. These studies suggest the possibility of an early programming of chronotype and they elaborate the spectrum of influences that impact long-term outcomes of premature birth.

Keywords: VLBW, preterm, chronotype, actigraphy, MEQ, sleep midpoint, MSFsc, HRQoL, 15D instrument

Tiivistelmä

Tausta. Ennenaikainen syntymä, eli syntyminen ennen 37 raskausviikkoa, voi olla haasteellinen alku elämälle. Maailmanlaajuisesti se on tavallisin alle viisivuotiaiden kuolemansyy, ja riski on sitä suurempi, mitä pienempi lapsi on. Suurin osa keskosista selviää ilman komplikaatioita ja viettävät normaalia elämää, kun taas toisilla on edessään enemmän haasteita. Vuosikymmenien pituiset seurantatutkimukset ovat osoittaneet ongelmia terveyden eri osa-alueilla, etenkin ns. pikkukeskosilla, joiden syntymäpaino on alle 1500 g. Monia keskosuuden pitkäaikaisvaikutuksia on tutkittu yksityiskohtaisesti, mutta toiset, kuten uni ja kronotyyppi, ovat saaneet vähemmän huomiota. Kronotyyppi kuvastaa sitä, mihin aikaan vuorokaudesta ihminen on virkeimmillään ja milloin mielellään lepää. Se on sisäinen vuorokausirytmin ilmentymä, ja ihmisiä, joilla on aikainen tai myöhäinen kronotyyppi, kutsutaan aamu- tai iltavirkuiksi. Kronotyyppi sekä unen kesto ja laatu ovat tärkeitä terveyttä ja hyvinvointia ennustavia tekijöitä. Iltavirkkuuteen ja huonoon uneen liittyvät ongelmat, kuten mielenterveyden ongelmat ja sydän- ja aineenvaihduntasairauksien riskitekijät, ovat tavallisia myös pikkukeskosilla. Tämä herättää kysymyksen, ovatko myöhäinen kronotyyppi ja uni yhteydessä keskosuuteen. Riskiraskauksien ja keskosten hoidon innovaatiot 1970 ja -80-luvuilla paransivat pikkukeskosten eloonjäämisennustetta huomattavasti, ja yksi keskeinen kysymys on, vaikuttavatko tuolloin syntyneiden keskosten alkutaipaleen vaikeudet heidän aikuisikäiseen elämänlaatuunsa.

Tavoite. Väitöskirjan tavoitteena oli tutkia ennenaikaisen syntymän ja pikkukeskosuuden yhteyttä aikuisiän kronotyyppiin, unen pituuteen ja laatuun sekä elämänlaatuun.

Menetelmät. Väitöskirjan tutkittavat kuuluvat johonkin neljästä syntymäkohortista, joissa on ennenaikaisesti syntyneitä keskosia ja täysiaikaisina syntyneitä verrokkeja. Pikku-k-tutkimuksen (Helsinki Study of VLBW Adults) tutkittavat ovat pikkukeskosia, jotka syntyivät vuosina 1978-85 ja hoidettiin Lastenklinikan vastasyntyneiden teho-osastolla. ESTER:in (Ennenaikainen syntymä, raskaus ja lapsen terveys aikuisiässä) ja AYLS:n (Arvo Ylppö Longitudinal Study) keskoset ovat syntyneet koko ennenaikaisuuden kirjosta, suurin osa hieman ennenaikaisina, raskausviikoilla 34-36. ESTERin tutkittavat on kutsuttu Pohjois-Suomen syntymäkohortista sekä Terveyden ja Hyvinvoinnin Laitoksen syntymärekisteristä, ja ovat syntyneet vuosina 1985-89. AYLSn keskoset syntyivät vuosina 1985-86, ja saivat hoitoa joko Lastenklinikan vastasyntyneiden teho-osastolla tai syntymäsairaalan lastenosastolla kymmenen päivän

sisällä syntymästä. Pikku-k-sisarustutkimuksen pikkukeskoset ovat osittain peräisin edellisestä Pikku-k- (1978-85) ja ESTER-tutkimuksesta (1987-89), mutta suurin osa värvättiin THL:n syntymärekisterin kautta. Nämä uudet osallistujat syntyivät vuosina 1987–90 Turun tai Tampereen yliopistollisessa sairaalassa tai Helsingin ja Uudenmaan sairaanhoitopiirissä. Näiden pikkukeskosten verrokkeina toimivat tutkittavien omat täysiaikaisena syntyneet sisarukset.

Käytimme aktigrafi-kiihtyvyysantureita tutkiaksemme unen ajoittumista, kestoa ja laatua. Keskeisin objektiivisen kronotyypin mitta oli univajeella korjattu unen keskikohta, kun taas subjektiivista kronotyyppiä mitattiin Morningness-Eveningness Questionnaire-kyselykaavakkeella. Elämänlaatua mitattiin 15D kyselylomakkeella.

Tulokset. Väitöskirjan ensimmäinen tutkimus vertasi aktigrafiatuloksia 40 aikuisen pikkukeskosen ja 35 verrokin välillä Pikku-k-kohortissa. Tutkittavat olivat iältään keskimäärin 25.0 vuotta (keskihajonta 2.2). Tutkimus osoitti, että pikkukeskosilla oli verrokkeja huomattavasti aikaisempi unen keskikohta (65 min, 95% luottamusvälit 14-116 min, $p = 0.013$). Unen kestossa tai laadussa ei ollut eroa.

Toinen tutkimus vertasi Pikku-k-sisarustutkimuksen aktigrafiatuloksia 63 pikkukeskosen ja 60 sisarusverrokin välillä (53 kokonaista paria). Tutkittavat olivat iältään 29.8 vuotta (keskihajonta 4.1). Unen keskikohta oli aikaisempi pikkukeskosilla (46 min, 95% luottamusvälit 16-77 min, $p = 0.004$). Unen kestossa tai laadussa ei ilmennyt eroja tässäkään tutkimuksessa.

Kolmas tutkimus yhdisti ESTER:in ja AYLS:n tutkittavat, ja vertasi hieman ennenaikaisesti syntyneiden (raskausviikoilla 34-36, $n = 165$), että aikaisemmin syntyneiden (<34 raskausviikkoa, $n = 83$) keskosten aktigrafidataa täysiaikaisena syntyneiden verrokkiryhmään ($n = 346$). Tutkittavat olivat iältään 24.3 vuotta (keskihajonta 1.3). Kronotyypissä, unen kestossa tai laadussa ei todettu eroa ryhmien välillä. Lisäksi 688 ESTER-tutkimuksen osallistujaa vastasi Morningness-Eveningness Questionnaire -kyselyyn, eikä kronotyypissa ilmennyt eroja.

Neljäs tutkimus vertasi elämänlaatua Pikku-k-syntymäkohortin 164 pikkukeskosen ja 172 verrokin välillä. Tutkittavat olivat iältään 22.5 vuotta (keskihajonta 2.1). Suorassa ryhmien välisessä vertailussa ei ilmennyt eroja, mutta alaryhmien vertailussa nousi esille kiinnostavia löydöksiä. Pikkukeskosilla, jotka olivat syntyneet pienipainoisina raskausviikkoihinsa nähden (alle -2 keskihajontayksikköä keskiarvosta), oli huonompi

elämänlaatu verrattuna pikkukeskosiin, jotka syntyivät viikkoihin nähden normaalipainoisina (0.911 ja 0.939, p = 0.039). Tämä johtui mahdollisesti siitä, että ”normaalipainoisilla” pikkukeskosmiehillä oli verrattaen hyvä elämänlaatu, kun taas pienipainoisilla pikkukeskosnaisilla oli yllättävän huono elämänlaatu.

Päätelmät. Pikkukeskosina syntyneillä aikuisilla todettiin varhaisempi kronotyyppi kuin täysiaikaisena syntyneillä verrokeilla. Löydös rajoittui pikkukeskosiin; lievemmin ennenaikaisesti syntyneiden ryhmien vertailu verrokkiryhmään ei paljastanut eroja. Unen kestossa tai laadussa ei todettu eroja, eikä pikkukeskosilla ollut ryhmätasolla huonompaa elämänlaatua, vaikka suhteellisen syntymäpainon alaryhmissä olikin eroja. Tutkimustulokset viittaavat siihen, että hyvin ennenaikainen syntymä voisi olla yhteydessä myöhemmän iän vuorokausirytmiin.

Sammanfattning

Bakgrund. En prematur födsel, dvs före graviditetsvecka 37, kan vara en svår början på livet. Globalt sett är prematuritet den ledande orsaken till död hos barn under fem år, och prognosen är sämre ju mindre barnet är. De flesta prematurer överlever utan grava funktionsnedsättningar, men decennierlånga uppföljningsstudier har påvisat subtila svårigheter inom olika områden av hälsa och välfärd, speciellt hos s.k. små prematurer med en födelsevikt på under 1500 g. Dessa studier har beskrivit många långtidsresultat i detalj, medan vissa viktiga forskningsområden, som t.ex. sömn och kronotyp, har uppmärksammats mindre. Kronotyp beskriver den personliga föredragna dygnsrytmen, dvs. när under dygnet man helst är aktiv eller sover. Det är en manifestation av den inre biologiska klockan och människor med tidiga och sena kronotyper kallas morgonlärkor och nattugglor. Kronotyp, sömnlängd och -kvalitet är viktiga faktorer för hälsan, och studier har visat att dålig sömn och en sen kronotyp är associerade med liknande svårigheter som prematurer upplever, t.ex. sämre mental hälsa och ogynnsam kardiometabolisk profil. Det väcker frågan om dålig sömn eller en sen kronotyp är associerade med prematuritet. Nya forskningsfrågor gällande prematuritet utvidgar vårt förstående av fenomenet, men vissa fundamentala frågor behöver periodiska uppdateringar. En sådan fråga är om överlevare av tidig prematur födsel, med alla sina svårigheter, ändå lever ett fullvärdigt liv?

Mål. Denna avhandling undersökte om prematuritet, med betoning på små prematurer, är associerad med kronotyp, sömnlängd, -kvalitet eller hälsorelaterad livskvalitet i vuxen ålder.

Metoder. Avhandlingens studier undersökte vuxna prematurer och fullgångna kontroller från fyra olika, dels överlappande kohorter. De små prematurerna från Helsinki Study of VLBW Adults (HeSVA) vårdades på Barnklinikens neonatala intensivavdelning under perioden 1978-85. ESTER-deltagarna är sammanslagna från Northern Finland Birth Cohort 1986 och en kohort med deltagare som föddes i samma område under åren 1987-89. AYLS (Arvo Ylppö Longitudinal Study) är en mångcenteruppföljningsstudie av unga vuxna som under åren 1985-86 inom tio dagar efter sin födsel i Nyland sköttes på Barnklinikens neonatala intensivavdelning eller förlossningssjukhusets barnavdelning. Prematurerna från ESTER- och AYLS-studierna är från hela spektrumet av förtidsbörd, av vilka största delen föddes lindrigt prematura, dvs. under graviditetsveckorna 34-36. Syskonstudien består av små prematurer och deras fullgångna syskon. Prematurerna

rekryterades dels från de tidigare studierna HeSVA (1978-85) och ESTER (1987-89), och dels rekryterades nya deltagare som identifierades från födelseregistret som upprätthålls av Institutet för hälsa och välfärd. De nya deltagarna föddes under perioden 1987-90 på universitetssjukhusen i Åbo och Tammerfors och i Helsingfors och Nylands sjukvårdsdistrikt.

Denna avhandling använde accelerometrar (s.k. aktigrafer) för att objektivt mäta sömnlängd, -kvalitet och när sömnen ägde rum. Det huvudsakliga måttet för objektiv kronotyp var sömnens mittpunkt korrigerad för sömnbrist. Subjektiv kronotyp mättes med frågeformuläret Morningness-Eveningness Questionnaire och livskvalitet mättes med 15D frågeformuläret.

Resultat. Studie I jämförde aktigrafidata mellan 40 små prematurer och 35 kontroller i HeSVA-kohorten. Deltagarnas genomsnittliga ålder var 25,0 år (SD 2,2). Studien upptäckte att prematurerna hade en signifikant tidigare mittpunkt för sömnen (65 min, 95% CI 14 till 116 min, p = 0,013) än kontrollerna. Ingen skillnad i sömnlängd eller -kvalitet upptäcktes.

Studie II jämförde aktigrafidata mellan 63 små prematurer och 60 fullgångna syskon (53 hela par). Deltagarnas genomsnittliga ålder var 29,8 år (SD 4,1). Igen hade de små prematurerna en tidigare mittpunkt för sömnen (46 min, 95% konfidensintervallerna 16 till 77 min, p = 0,004), men ingen skillnad i sömnlängd eller -kvalitet.

Studie III jämförde aktigrafidata mellan kontroller (n = 346) och två grupper av prematurer från den sammanslagna ESTER-AYLS-kohorten: lindrigt prematura (34 till 36 graviditetsveckor, n = 165), eller tidigt prematura (<34 graviditetsveckor, n = 83). Den genomsnittliga åldern var 24,3 år (1,3). Studien uppdagade inga skillnader i objektiv kronotyp, sömnlängd eller -kvalitet. Dessutom fyllde 688 ESTER-deltagare i Morningness-Eveningness Questionnaire-frågeformuläret för att bedöma subjektiv kronotyp. Inga skillnader mellan grupperna uppdagades heller via formulären.

Studie IV jämförde den hälsorelaterade livskvaliteten mellan 164 små prematurer och 172 kontroller i HeSVA-kohorten. Den genomsnittliga åldern var 22,5 år (SD 2,1). I det stora hela skiljde sig inte grupperna, men analysen av undergrupperna avslöjade att små prematurer, vars födelsevikt dessutom var liten för graviditetsveckorna (under -2 SD), hade sämre livskvalitet än små prematurer med adekvat födelsevikt. Skillnaden mellan grupperna berodde möjligen på att män födda som små prematurer med adekvat vikt

rapporterade rätt god livskvalitet, medan prematurkvinnor med relativt sett liten födelsevikt rapporterade sämre livskvalitet.

Slutsatser. I motsats till förväntningarna visade det sig att prematuritet är associerad med en tidigare kronotyp. Detta fynd verkar enbart gälla små prematurer och inte prematurer från lindrigare förtidsbörd. Prematuritet verkar inte påverka sömnlängd, -kvalitet eller hälsorelaterad livskvalitet, även om det fanns klara skillnader i livskvalitet i undergrupperna. Dessa studier antyder att tidig prematuritet kan vara associerad med kronotyp i vuxen ålder.

Table of contents

List of original publications

I Björkqvist J, Paavonen J, Andersson S, Pesonen A-K, Lahti J, Heinonen K, Eriksson J, Räikkönen K, Hovi P, Kajantie E, Strang-Karlsson S. 2014. Advanced sleep–wake rhythm in adults born prematurely: confirmation by actigraphy-based assessment in the Helsinki Study of Very Low Birth Weight Adults. Sleep Med. 15:1101–1106.

II Björkqvist J, Kuula J, Kuula L, Nurhonen M, Räikkönen K, Hovi P, Pesonen A, Kajantie E. Working title: "Chronotype in very low birth weight adults – a sibling study" (submitted).

III Björkqvist J, Pesonen A-K, Kuula L, Matinolli H-M, Lano A, Sipola-Leppänen M, Tikanmäki M, Wolke D, Järvelin M-R, Eriksson JG, Andersson S, Vääräsmäki M, Heinonen K, Räikkönen K, Hovi P, Kajantie E. 2018. Premature birth and circadian preference in young adulthood: evidence from two birth cohorts. Chronobiol Int. 35:555–564.

IV Björkqvist J, Hovi P, Pesonen A-K, Räikkönen K, Heinonen K, Järvenpää A-L, Eriksson JG, Andersson S, Kajantie E. 2018. Adults who were born preterm with a very low birth weight reported a similar health-related quality of life to their term-born peers. Acta Paediatr. 107:354–357.

Abbreviations

AGA	Appropriate for gestational age
APIC	Adults born preterm international collaboration
AYLS	Arvo Ylppö Longitudinal Study
B	Regression coefficient
CI	Confidence interval
CP	Cerebral palsy
DLMO	Dim-light melatonin onset
ELBW	Extremely low birth weight (<1000 g)
ESTER	Ennenaikainen syntymä, raskaus ja lapsen terveys aikuisiässä
GWAS	Genome-wide association study
HeSVA	Helsinki Study of Very Low Birth Weight Adults
HRQoL	Health-related quality of life
MEQ	Morningness-Eveningness Questionnaire
MCTQ	Munich Chronotype Questionnaire
MSFsc	Midsleep on free days, sleep debt-corrected
NICU	Neonatal intensive care unit
NREM	Non-rapid eye movement
NSI	Neurosensory impairment
PSG	Polysomnography
QoL	Quality of life
REM	Rapid eye movement
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SGA	Small for gestational age
VLBW	Very low birth weight (<1500 g)
VP	Very preterm (<32 weeks)
WHO	World Health Organization

1. INTRODUCTION

Practically all life on earth is governed by two sets of clocks: the solar clock and the inner biological clock. A third clock exists, however, which regulates human life, namely the social clock. How well we are adjusted to these clocks is important, but complicated, because they are not necessarily synchronized, nor running at the same speed. Having a later circadian rhythm ("chronotype"), in essence being a "night owl", has been linked to a host of adverse outcomes, such as higher blood pressure, more dysglycaemia, and depression (Merikanto, Lahti, Puolijoki, et al. 2013; Merikanto, Lahti, Kronholm, et al. 2013). "Night owls", especially when compared to "morning larks", also exercise less (Wennman et al. 2015; Wong et al. 2015). Up to half of the variation in chronotype seems genetically determined (Koskenvuo et al. 2007), but not everything written in our genes is necessarily read. The Developmental Origins of Health and Disease hypothesis postulates that perinatal or even prenatal conditions program trajectories of health that might emerge decades later (Barker 2007). This hypothesis has gained support from research on survivors of preterm birth, especially those with a very low birth weight (VLBW) of less than 1500 grams. In agreement with this developmental programming hypothesis, survivors of very or extremely preterm births suffer from adverse outcomes such as higher blood pressure, more dysglycaemia, depression, and anxiety (Nosarti et al. 2012; Hovi et al. 2016; Morrison et al. 2016; Mathewson et al. 2017; Mathewson et al. 2017); in addition, they exercise less than do term-born controls (Kajantie, Strang-Karlsson, et al. 2010). The similarity of outcomes of a later chronotype and of a VLBW preterm birth raises a question: are these somehow connected? Does preterm birth program a later chronotype?

The primary aim of this thesis was to investigate whether preterm birth is associated with adult chronotype, both in VLBW and later-born preterm populations. The secondary aim was to investigate whether prematurity impacts sleep at adult age. The final objective was to investigate whether a VLBW birth affects the arguably most important outcome: quality of life.

2. REVIEW OF THE LITERATURE

2.1. Prematurity

"Let us change the future for millions of babies born too soon, for their mothers and families, and indeed for entire countries. Enabling infants to survive and thrive is an imperative for building the future we want."

> Ban Ki-Moon, United Nations Secretary-General
> "Born Too Soon – The Global Action Report on Preterm Birth" (March of Dimes et al. 2012)

Every year almost 15 million infants are born preterm. Having spent less than 37 weeks in the safety of the womb they are thrust underdeveloped into the world, the nourishing lifeline to their mothers severed. The survival of these vulnerable infants has improved dramatically during the last five decades due to the enormous advances in neonatology and prenatal care; today even children born four months early in high-income countries have better chances than a coin toss to survive. Globally preterm birth is the leading cause of death in young children, however, which is why the World Health Organization (WHO) has focused on the problem. Notably the Secretary-General's summon for action not only called for improved survival of these infants, but also that they should *thrive*. This is an important addition, because lifelong disability is the fate for some survivors, and decades-long cohort studies show that even those spared apparent detriments during the precarious beginning of their lives show subtle signs of impairment as adults. This first chapter of the thesis review attempts to describe the phenomenon of preterm birth, and to underline the magnitude of the problem, both regarding immediate survival and the lingering effects that might impede flourishing in later life.

2.1.1. Human birth and prematurity – an evolutionary perspective

Compared to other mammals and primates, the birth of a human child is a perilous endeavour. WHO estimates that 270 000 mothers suffered pregnancy-related deaths in 2010, and that 73% of maternal deaths in 2003-09 were directly due to obstetric causes (World Health Organization 2012; Say et al. 2014). An estimated 2.7 million babies died during the neonatal period in 2015, with almost 60% explained by either prematurity or intrapartum-related events (Liu et al. 2016). Why is human birth so often a medical emergency? A classical evolutionary theory, the "obstetric dilemma", maintains that two strong counterproductive evolutionary forces have caused the current state, namely the fitness advantages of bipedal movement and having a large brain. These two forces require different anatomical dimensions of the maternal pelvis (Washburn 1960; Wittman and Wall 2007): walking on two legs is easier with decreased pelvis height and increased mediolateral breadth, whereas giving birth to large-headed infants requires increased anteroposterior dimensions. As a consequence the children of *Homo Sapiens* must rotate in the birth canal to enter the world (Wells et al. 2012). Arguably, the adaptation to the "obstetrical dilemma" has been shortened gestation, so that compared to other new-born primates, humans are quite, but not totally helpless (secondarily altricial) at birth. Proposed proof for this hypothesis has been that neonatal brain size relative to adult size is much smaller in humans (30%) than in chimpanzees (40%), and that the period of rapid brain development occurs later in humans (Dunsworth 2018).

The hypothesis of the obstetrical dilemma has received critique during the last decade, however (Dunsworth 2018). The claim that a specific pelvis type is required for efficient bipedalism is contradicted by studies showing that different pelvises do not incur mentionable penalties to running (Warrener et al. 2015). Also, alternative explanations for the timing of human parturition has emerged, such as the energetics of gestation and fetal growth hypothesis (Dunsworth et al. 2012), which suggests that if gestation would continue longer, the exponentially increasing fetal metabolic demands would exceed the mother's maximum sustainable metabolic rate. Further, comparative studies show that humans do not have a uniquely short gestation period. If the human cut-off for preterm birth (37 weeks, 92.5% of term) is applied to other placental mammals, all but horses, goats, and rodents display preterm births and similar variations in gestation length. Also, the human gestational length seems to scale with body mass like other mammals (Phillips et al. 2015). So, what other reasons than the classical obstetrical dilemma can explain the

difficult childbirth humans experience? Some possible alternative explanations are more ecological, such as the emergence of agriculture which possibly 1) decreased the average intake of protein, leading to decreased stature, 2) increased the glycaemic load, leading to increased size of the offspring, and 3) increased the infectious burden, possibly leading to survival of more adipose babies (Wells et al. 2012).

While these anthropological and evolutionary studies are not directly practical, investigation of ancient causes for current problems might uncover possible solutions, and comparing the human condition to that of closely related animals could discover useful animal models, or at least reveal what makes human birth so human.

2.1.2. What defines a preterm birth?

WHO defines preterm birth as less than 37 completed weeks of gestation or fewer than 259 days since the first day of the last menstrual period (March of Dimes et al. 2012). While estimation based on menstrual period is low-cost and globally applicable, ultrasonographic estimation is preferred due to variability in menstrual cycle length. WHO defines term birth as between 37 and <42 weeks of gestation. Birth after this period is called post term. Any delivery at ≥22+0 weeks or ≥500 g birth weight, or whenever the new-born shows signs of life is defined as a birth. Both a child born at 23 and 36 weeks are by definition preterm but the wide variation in maturity warrants further categories, either based on gestation length or birth weight. The WHO prematurity categories based on gestation length are, in ascending order: extremely preterm <28 weeks, very preterm 28 to <32 weeks, and "moderate to late preterm birth" 32 to <37 weeks. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics further define "late preterm" as between 34 and <37 weeks of gestation, which represents over 70% of all preterm births (Figures 1 and 2, Raju et al. 2006; Engle et al. 2007; Vuori & Gissler 2016).

Figure 1. Proportions of Finnish preterm live births in 2015 according to gestational age (Vuori and Gissler 2016, figure by the author). The overwhelming majority of preterm infants are born late preterm.

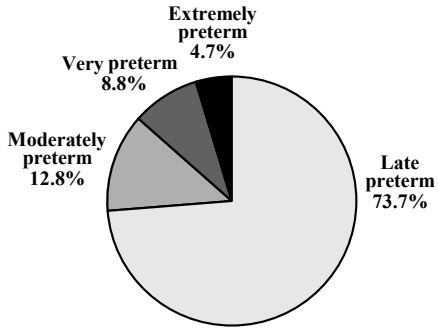
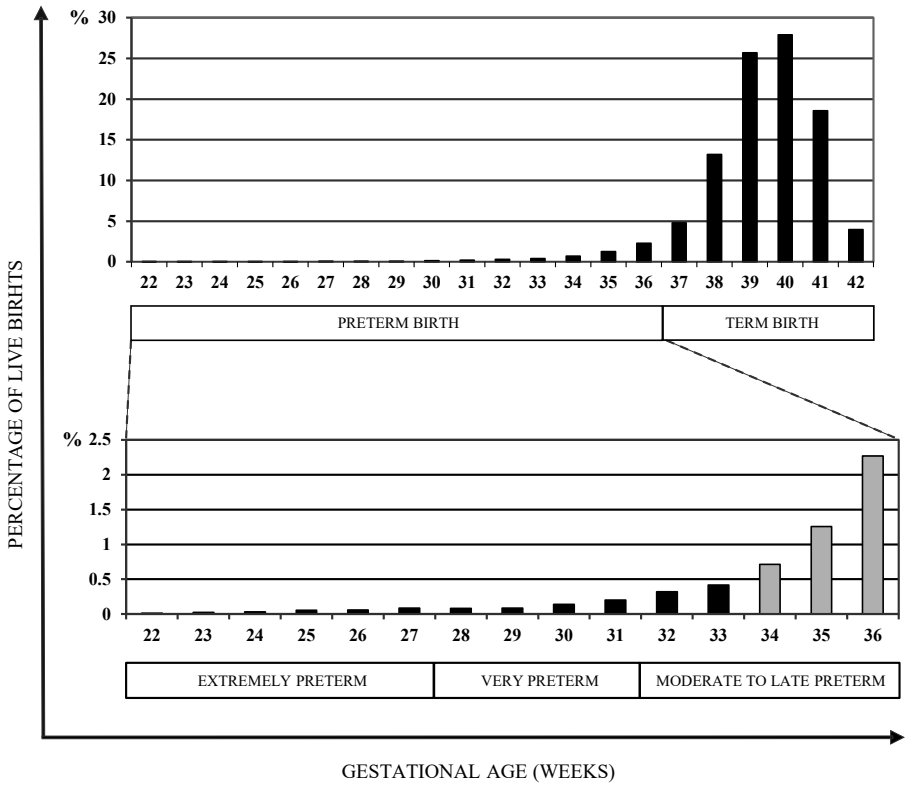
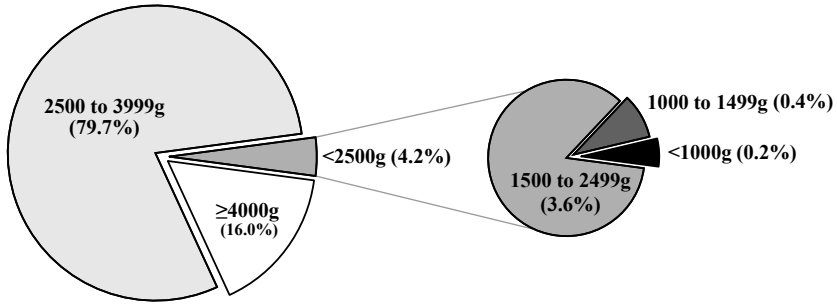


Figure 2. Finnish perinatal statistics of live-born babies by gestational weeks in 2015 (Vuori and Gissler 2016, figure by the author). The light grey columns indicate late preterm births. In 2015, 5.7% of all live births in Finland were preterm.



Another way of grading preterm birth is by birth weight. In ascending order, the categories are: extremely low birth weight (ELBW, <1000 g), very low birth weight (VLBW, <1500 g), and low birth weight (LBW, <2500 g).

Figure 3. Proportions of Finnish live-born babies in 2015 by birth weight (Vuori and Gissler 2016, figure by the author). Unknown (0.1%) not represented. Very low birth weight (<1500 g) births accounted for about 0.6% of all live births.



Preterm birth is not exactly the same thing as *premature* birth, however, because also term-born infants can suffer from impaired maturation, so additional metrics prove useful for labelling suboptimal growing environments. Intrauterine growth retardation describes poor infant growth and thereby poor conditions, but the diagnosis requires ultrasonographic investigation. An easier, but less accurate proxy is small for gestational age (SGA), which is based on the relative birth weight of the infant compared to population statistics, adjusted for age and sex. The definition for SGA has varied from less than the 3rd percentile of the population, to less than the 10th percentile (Zeve et al. 2016). This thesis uses the most widely employed definition (Clayton et al. 2007): birth weight and/or length under -2 standard deviations of the population mean, adjusted for age and sex, based on Finnish birth statistics (Pihkala et al. 1989).

2.1.3. What are the causes of preterm birth?

There are three precursors to preterm birth: iatrogenic intervention due to fetal or maternal indications (30-35% of the cases), spontaneous preterm labour with intact membranes (40-45%), and preterm premature rupture of the membranes (25-30%). Birth caused by spontaneous preterm labour and preterm premature rupture of membranes is called a spontaneous preterm birth (Goldenberg et al. 2008). The pathogenesis of spontaneous preterm labour is a mystery; it might be the result of external insults or an earlier activation of the normal parturition process. Two hypotheses are inflammatory decidual activation and fetal cortisol disrupting the maternal oestrogen/progesterone ratio (Goldenberg et al. 2008). Because the exact mechanism for preterm labour remains unknown it is useful to consider preterm labour a syndrome with many possible causes. Some risk factors have been established, although half of preterm births occur in pregnancies without any (Menon 2008):

Maternal risk factors. Both a low and high maternal age (<20 or >36 years), and a low and high maternal body mass index (<18.5 or >25) seem to increase the risk for a spontaneous preterm birth (Bhattacharya et al. 2010; Cnattingius et al. 2013; Shaw et al. 2014). Current life situation also has an influence, with a lower socio-economic status increasing the risk (Smith et al. 2007), and also possibly working long hours (van Melick et al. 2014), performing heavy lifting (Knudsen et al. 2017), and smoking tobacco (Ion and Bernal 2015). Several chronic diseases such as thyroid disease, asthma, diabetes, hypertension, and depression also increase the risk for preterm birth (Goldenberg et al. 2008).

Pregnancy history and characteristics. An interpregnancy spacing under 12 months and over 36 months seems to increase the odds for preterm birth (Shachar et al. 2016), as does a previous preterm delivery: a mother whose previous singleton birth was preterm has an absolute recurrence risk of 20% (Kazemier et al. 2014). Multiple pregnancies increase the risk of preterm birth, as nearly 60% of twins are born preterm, and for 40% this will be due to spontaneous labour or preterm premature rupture of membranes (Goldenberg et al. 2008).

Infection and inflammation. Infection is an important cause for preterm birth, regardless of whether the infection is located in the vagina, decidua, chorioamnion, the amniotic cavity, or even the fetus itself. Intra-uterine infection might account for 25-40% of preterm births (Goldenberg et al. 2008), and bacterial vaginosis seems to double the

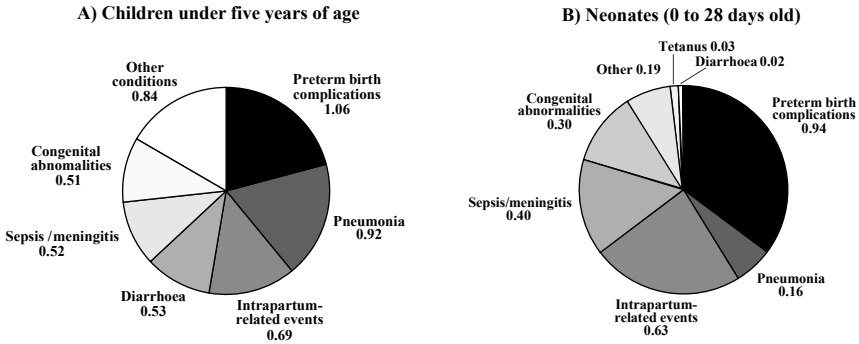
risk for spontaneous preterm delivery (Goldenberg et al. 2000). The routes for invasion can be an ascent from the vagina and cervix, bacteraemia through the placenta, iatrogenic invasion, or a retrograde spread through the fallopian tubes. It is thus possible that maternal systemic bacteraemia can allow even non-genital infections, such as pneumonia, appendicitis, and periodontological infections to reach the amnion (Goldenberg et al. 2008).

Genetics. The observed familial tendency for preterm births has understandably insinuated some genetic determinants. Women are more likely to experience preterm labour if their grandparents, mothers, or sisters have also done so (Porter et al. 1997; Winkvist et al. 1998; Bhattacharya et al. 2010), and some studies have suggested a heritability of ~30% (Zhang et al. 2018). The genetic influence seems the be mostly explained by maternal genetics instead of paternal (Wilcox et al. 2008; Boyd et al. 2009). The study of specific genes involved in preterm birth is inherently difficult due to inaccuracy of gestational age determination, variable clinical presentations, and because birth timing is influenced by both the maternal and fetal genome and their interaction (Zhang et al. 2018). The candidate gene approach has provided inconclusive results regarding meaningful polymorphisms (Sheikh et al. 2016), possibly implying that preterm birth is influenced by many genes with small effect sizes. To overcome sample size problems an international collaboration performed a two-stage genome-wide association study (GWAS), partly based on data from 23andMe (Zhang et al. 2017), and identified six genomic loci robustly associated with preterm birth (*EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5*, and *RAP2C*). Although this finding was important, these loci explained less than 1% of the phenotypic variance in gestational duration or preterm birth risk, which implies that much remains unknown (Zhang et al. 2018).

2.1.4. Global epidemiology

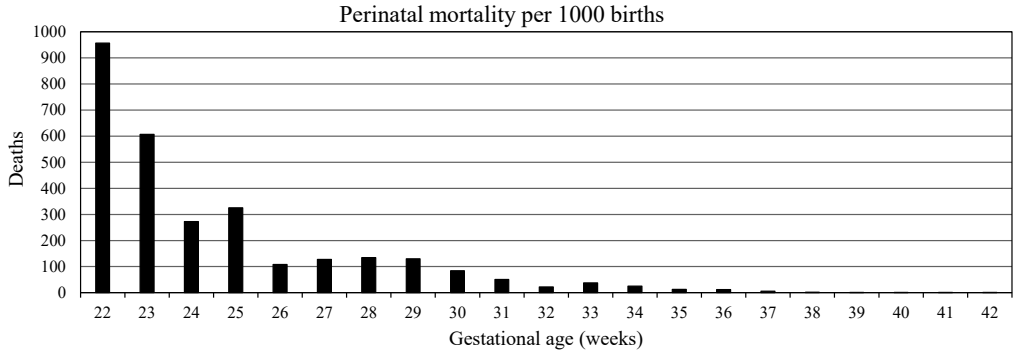
An estimated 14.8 million children were born prematurely in 2014, equalling 10.6% of all live births, and over 15% of them occurred before 32 weeks of gestation (Chawanpaiboon et al. 2019). Complications due to preterm birth are the leading cause of death in children under the age of 5, with an estimated 1.1 million deaths in 2015 (Figure 4, Liu et al. 2016). Socio-economic and regional factors influence these statistics significantly; the ten countries with the highest childhood mortality account for ~60% of the global death toll (Liu et al. 2016).

Figure 4. Causes of death globally in millions in a) children under five years b) neonates (Liu et al. 2016, figure by the author). Preterm birth is the main cause of death in both groups.



WHO estimates that wide-spread implementation of low-cost interventions like antenatal corticosteroids and "Kangaroo care" could prevent >75% of these deaths (Blencowe et al. 2012; March of Dimes et al. 2012), but although basic interventions are important to reduce the bulk of deaths, modern neonatal intensive care is paramount for the survival of those born smallest. Over 90% of infants born extremely preterm (<28 weeks) in low-income countries die within days, whereas less than 10% do so in high-income countries. With neonatal intensive care the 50% survival rate is at 34 weeks in low-income countries, and 24 weeks in high-income countries: a difference of over two months (March of Dimes et al. 2012, Figure 5 shows perinatal mortality in Finland).

Figure 5. Perinatal mortality per 1000 births in Finland 2015, according to gestational age in weeks (Vuori and Gissler 2016, figure by the author). Perinatal mortality increases markedly at lower ages.



Despite advances in technology and medical care, preterm birth rates have not uniformly declined: a recent WHO estimate for the period 2000-14 with data from 38 countries showed that the rate increased in 26 countries, and decreased in 12 (Chawanpaiboon et al. 2019). This can partially be explained by a greater rigor in differentiating extremely preterm livebirths from stillbirths (Blencowe et al. 2012), and that fetal distress is noticed earlier, which prompts more caesarean sections at earlier weeks. Such interventions reduce stillbirths and increase preterm births in the statistics.

2.1.5. Outcomes of preterm birth

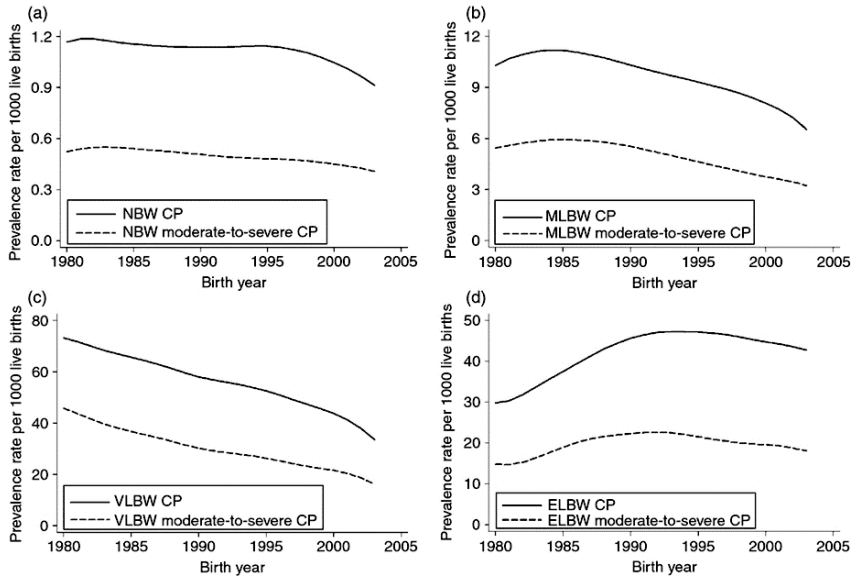
This thesis section will outline outcomes of preterm birth, with an emphasis on VLBW adults. Chronotype, sleep, and health-related quality of life are addressed in later independent chapters, as they form the central topics of this thesis.

Survival. Survival of those born smallest has steadily improved for decades. For VLBW babies born in 1978-85 and treated in the neonatal intensive care unit (NICU) of the Children's Hospital at Helsinki University Central Hospital (the time and place for the subjects of Study I and IV), the mortality rate was 29% (Järvenpää and Granström 1987). Between the 1970s and 1990s the survival rate of the smallest preterms (<26 weeks or ≤800 g) born in western high-income countries increased annually by about 2% (Lorenz et al. 1998), possibly due to the protective effects of antenatal corticoids and postnatal surfactant. The use of these two aids increased dramatically during the 1990s, with a threefold increase in use of antenatal steroids and an increase from 49% to 62% in the use of surfactant (Horbar et al. 2002). For infants with a birth weight of 500 to 1500 g, data from the Vermont Oxford Database show that the mortality rate continued to fall in the early 1990s and it plateaued for the rest of the decade: an overall decrease from 17.7% to 15.1% (Horbar et al. 2002). Between the years 2000-09 the rate has continued declining, from 14.1% to 12.5% in the same group (Horbar et al. 2012). Data from ten national neonatal networks from the years 2007-13 show that among VLBW babies born between weeks 24 and 29, the mortality rate before discharge was 13% (Helenius et al. 2017).

Cerebral palsy (CP). Large register studies have shown that during the last decades the prevalence of CP due to preterm birth has either not changed (Oskoui et al. 2013), or has been in decline (Sellier et al. 2016). The Surveillance of Cerebral Palsy Network has demonstrated that between 1980-2003, CP prevalence decreased in VLBW children from 70.9 per 1000 live births to only 35.9 (Sellier et al. 2016). For ELBW infants, the increased survival might have incurred a cost of increased morbidity during the 1980s and early 1990s (Figure 6). The pioneering treatments during that period allowed continually lower thresholds of viability; smaller and smaller children survived, but not necessarily without problems. Also, treatments like postnatal corticosteroids were later suspected to cause neurodevelopmental harm (DeMauro et al. 2014; Doyle et al. 2014). But even the rate of CP in the ELBW group has since been in decline, at least in Europe (Sellier et al. 2016).

Figure 6. (a) Prevalence rate of cerebral palsy (CP) for children born with a birthweight ≥2500g, per 1000 live births. (b) Prevalence rate of CP for children born with a birthweight between 1500g and 2499g, per 1000 live births. (c) Prevalence rate of CP for children born with a birthweight between 1000g and 1499g, per 1000 live births. (d) Prevalence rate of CP for children born with a birthweight below 1000g, per 1000 live births. NBW, normal birthweight; MLBW, moderately low birthweight; VLBW, very low birthweight. ELBW, extremely low birthweight.

From: Elodie Sellier, Mary Jane Platt, Guro L Andersen, et al. 2016. "Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003". Developmental Medicine & Child Neurology. Volume 58, Issue 1, pages 85-92, 2015 DOI: 10.1111/dmcn.12865 http://onlinelibrary.wiley.com/doi/10.1111/dmcn.12865/full#dmcn12865-fig-0003. Reused with permission from John Wiley and Sons, license #4516960792552.



Sensory impairments. A sensory impairment commonly associated with premature birth is blindness, often caused by retinal damage due to iatrogenic hyperoxia; one review estimated that blindness prevalence ranges from 2 to 13% in adult populations born VLBW or ELBW (Hack 2009). In a blood pressure meta-analysis of nine cohorts with participants born VLBW or smaller, the prevalence of at least stage 3 retinopathy (severely abnormal blood vessel growth) varied between 3.2 and 14.7% (Hovi et al. 2016). In 2010, an estimated 20 000 preterm babies became blind or severely visually impaired due to retinopathy of prematurity (Blencowe et al. 2013). Deafness is also associated with prematurity, with a prevalence of 1 to 6% in adult VLBW or ELBW populations (Hack 2009).

Intelligence. The brain is particularly sensitive to insults like oxygen deprivation, which is also common in premature births, so long-term outcomes regarding intelligence and neurocognitive function are important. A study of the Copenhagen Perinatal Cohort had subjects perform intelligence tests at ages 19, 28, and 50, and found that subjects born <2500 g consistently scored >5 IQ points lower than those born 3500-4000 g (Flensborg-Madsen and Mortensen 2017). Fifteen points in IQ equals one standard deviation, so 5 points is about 0.33 SD. A meta-analysis comparing intelligence between low (<2500 g) and normal birth weight (≥2500 g) adolescents and young adults suggested that after adjustment for publication bias the low birth weight group scored ~5 points lower on IQ (Kormos et al. 2014). A recent meta-analysis of 23 studies showed that compared to term-born controls, adult preterms are less likely to attain a higher education, less likely to be employed, and more often receive social benefits (Bilgin et al. 2018). Studies on VLBW adults without major neurosensory impairment (NSI) have indicated lower IQ scores in the range of 0.3 to 0.55 SD (Pyhälä et al. 2011; Breeman et al. 2015). Understandably, if the analyses included impaired preterms the differences were larger.

Personality and mental health. Compared to term-born controls, the personality profile of VLBW or very preterm (VP, <32 weeks) adults tend to show higher levels of conscientiousness, agreeableness, and neuroticism, and more withdrawal, social avoidance, and anxiousness (Pesonen et al. 2008; Hertz et al. 2013; Eryigit-Madzwamuse et al. 2015). They are also more risk averse and introverted, they move from the family home and initiate sexual relationships at a later age, and are not as prone to use or misuse alcohol, tobacco or drugs (Kajantie et al. 2008; Hack 2009; D'Onofrio et al. 2013), although a Swedish register study has also suggested an increased risk for alcohol dependency (Nosarti et al. 2012). VLBW adults somewhat consistently report more internalizing and less externalizing behaviours: the Adults Born Preterm International Collaboration (APIC) reported in a meta-analysis of six VLBW/ELBW cohorts that preterm subjects reported more internalizing and avoidant personality problems, and less externalizing, rule breaking, intrusive behaviour, and less antisocial personality problems (Pyhälä et al. 2017). A Swedish cohort study based on psychiatric hospitalizations showed that, compared to term-born patients, those born at 32-36 weeks were 1.3 times more likely to have had a depressive disorder, and 2.7 times more likely to have had a bipolar disorder. Patients born <32 weeks were 2.9 times more likely to have had a depressive disorder (Nosarti et al. 2012). However, a study from the Bavarian

Longitudinal Study did not discover a difference in the prevalence of mood or anxiety disorders after adjustments in VLBW/VP adults (Jaekel et al. 2018).

Fitness. Relatively few studies have investigated physical activity in adults born preterm. One study in the Helsinki Study of VLBW Adults (HeSVA) compared objective physical activity in unimpaired VLBW ~25-year-olds to controls and did not find a difference (Kaseva et al. 2015), nor did a study on "early preterm" (<34 weeks) young adults (Tikanmäki, Tammelin, et al. 2017). VLBW adults have reported lower leisure-time physical activity in questionnaires (Kajantie, Strang-Karlsson, et al. 2010; Kaseva et al. 2012), however, as have young adults born early preterm (Tikanmäki, Kaseva, et al. 2017). Another study on young adults born <34 weeks showed poorer muscular and self-rated fitness (Tikanmäki et al. 2016). These studies indicate that adults born VLBW or early preterm seem to report less physical activity and lower fitness, but this has not always been captured with objective measurements.

Respiratory health. A common complication of premature birth is bronchopulmonary dysplasia, a chronic lung disease of prematurity, which depending on the definition has an incidence of 6-57% in preterm subjects (Hines et al. 2017). Impaired lung function is not restricted to subjects with this diagnosis, however. A recent APIC meta-analysis, containing individual participant data from 11 studies, showed that very preterm/VLBW subjects in late adolescence and young adulthood display clinically important reductions in airflow even without bronchopulmonary dysplasia (Doyle et al. 2019). Several other studies and meta-analyses have also confirmed the suggested relationship between lower birth weight/gestational age and chronic lung impairments (Lawlor et al. 2005; Saad et al. 2017; Näsänen-Gilmore et al. 2018). Sleep-disordered breathing is addressed in 2.3.4.

Cardiometabolic risk factors and disease. Ever since the pioneering work of David Barker on East Hertfordshire men born 1911-30 (Barker et al. 1989), early programming of cardiovascular health has been a focal point of the Developmental Origins of Health and Disease paradigm. Regarding risk factors, VLBW adults have consistently displayed higher blood pressure than controls (de Jong Femke et al. 2012; Parkinson et al. 2013), and the recent APIC meta-analysis of nine cohorts showed a 3.4 mmHg higher systolic and 2.1 mmHg higher diastolic blood pressure (Hovi et al. 2016). VLBW adults also both display a higher resting heart rate (Hovi et al. 2007) and higher diastolic pressure under duress (Pyhälä et al. 2009). Compared to controls, VLBW and ELBW adults display more insulin resistance, glucose tolerance, or dysglycaemia (Hovi

et al. 2007; Morrison et al. 2016). Some studies show that prematurity is associated with higher levels of low-density lipoproteins (Parkinson et al. 2013), but others do not (Kajantie and Hovi 2014). Two studies from 2016 utilized Mendelian randomization to study the effect of birth weight on cardiometabolic outcomes: Yeung et al. (2016) found that a higher genetically determined birth weight was possibly associated with lower risk for ischemic heart disease, and Wang et al. (2016) showed that a genetically lowered birth weight increased the risk for diabetes. As for body composition VLBW adults might have a lower lean body mass and a tendency for central adiposity (Kajantie and Hovi 2014), but the evidence in ELBW adults is clearer, indicating a lower lean mass, higher percent body fat, and similar waist circumference (Morrison et al. 2016).

Regarding actual manifest disease the results are more ambiguous. For diabetes the data indicate higher rates of disease in adult preterm subjects (Lawlor et al. 2006; Kaijser et al. 2009; Kajantie, Osmond, et al. 2010; Crump et al. 2011), but no clear link between gestational age and coronary heart disease has emerged, and instead poor fetal growth has been implicated (Koupil et al. 2005; Kaijser Magnus et al. 2008; Kajantie et al. 2015; Zöller et al. 2015). Regarding stroke, the evidence is contradictory (Koupil et al. 2005; Ueda et al. 2014; Kajantie et al. 2015).

Summary. These studies reveal that the long-term effects of very preterm birth are a nuanced affair. The challenging beginning might have left complications such as cerebral palsy, blindness, and deafness, but most are spared these impairments. Individuals born preterm can and do defy the notions outlined here, but on average the adult VLBW survivor is conscientious and careful, modestly impeded in intellectual pursuits, more ruminant than disruptive, and displays an unfavourable health profile. The lack of manifest coronary heart disease possibly demonstrates the importance of protective factors, such as the higher levels of conscientiousness, and lesser inclination for smoking and drinking.

2.2. Circadian rhythm and chronotype

Circadian (/səːˈkeɪdɪən/, latin *circa* about + *dies* day)

: being, having, characterized by, or occurring in approximately 24-hour periods or cycles (as of biological activity or function)

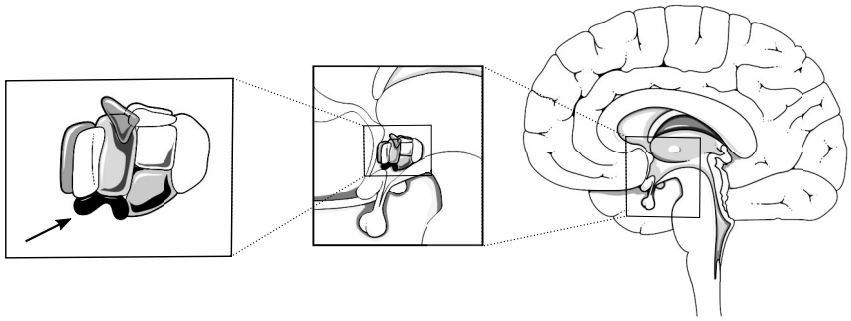
(The Merriam Webster Dictionary)

Subjected to eons of existential threat, life on earth has endured due to traits our ancient ancestors developed that increased chances for survival and reproduction. The environment has changed radically since our abiogenesis, but even the first assembly of living particles was born in a world with one unchanging change: the continuous cycle of day and night. It is thus hardly surprising that an evolutionarily advantageous ~24h circadian machinery is found within all three phylogenetic domains: in the substrate of germs and men (Woelfle et al. 2004; Edgar et al. 2012; Bhadra et al. 2017). This thesis chapter attempts to elucidate how this clock works in humans, how there is variation in our temporal preference, and what happens if we disregard the clock that ticks inside us.

2.2.1. Circadian rhythm in humans

A conceptual model of the human timekeeping system is that every living cell in the human body has an autonomous circadian rhythm that is driven by a molecular clock (see Figure 9, p. 43). These individual clocks would all be ticking away independently, like musicians deaf to their partners, were it not for a conductor. This role is played by the master clock, also known as the *central pacemaker*, which is a subset of neurons in the paired suprachiasmatic nucleus (SCN), situated on each side of the third ventricle in the anterior hypothalamus (Figure 7, Reppert & Weaver 2002).

Figure 7. Anatomical location of the suprachiasmatic nucleus. Figure by the author, modified from images provided by Smart Servier Medical Art (http://smart.servier.com), CC-BY 3.0 license.



The central pacemaker projects robust circadian signals to brain sites responsible for integrating sensory data and influencing many physiological processes, such as stress reaction, feeding behaviour, melatonin production, body temperature, heart rate, and blood pressure. The rhythm for the musical piece is thus transmitted from the central pacemaker to the *peripheral circadian clocks* in a hierarchical manner (Richards and Gumz 2012). The signalling structure is under study, but a variety of mechanisms seem to influence the peripheral circadian clocks, such as direct neuronal activation via the autonomous nervous system, neuroendocrine signalling via e.g. glucocorticoids, and more diffuse signalling such as body temperature and nutrient intake (Brown and Azzi 2013). Peripheral circadian clocks presumably exist in nearly all cells and tissues (Yoo et al. 2004), and they seem to display similar molecular clocks as the central pacemaker itself (Yagita 2001).

But how does the central pacemaker know what rhythm to conduct? Different signalling pathways influence it with external and possibly internal cues. During the day, sunshine activates light-sensitive cones, rods, and melanopsin in the retina of the eye. The neurosensory information travels along the retinohypothalamic and geniculothalamic tracts to the pacemaker cells of the SCN, where increased expression of clock genes seem to set the circadian clock (Challet et al. 2003; Yan 2009). Light is not the only *Zeitgeber* (german for "Timegiver") the central pacemaker listens to, but it is the most potent. Earlier conceptual models of the circadian system described the relationship between central and peripheral circadian clocks as a master-slave relationship, with no autonomous functioning in the periphery. Interestingly, more recent studies show that e.g. feeding and exercise timing can locally influence the peripheral circadian clocks in the liver, gut, and muscle (Tahara et al. 2017). The peripheral clocks might also send information back to the central pacemaker (Richards and Gumz 2012; Tahara et al. 2017), so in a sense the conductor might also listen to the musicians.

The facts that peripheral clocks can act in dyssynchrony to the central pacemaker, that the pacemaker can receive conflicting stimuli, and that many physiological processes behave differently depending on circadian timing have far-reaching implications regarding links between behaviour, circadian rhythm and health; not only does it matter what we eat and how much we exercise, but also *when* we do it (Plikus et al. 2013; Laermans and Depoortere 2016; Hower et al. 2018). These findings provide credence to the wisdom of good sleep hygiene, and possibly even archaic eating advice (Asher and Sassone-Corsi 2015), and they have real-world ramifications to those who live in circadian misalignment, such as shift workers.

''Eat like a king in the morning, a prince at noon, and a peasant at dinner.''

Maimonides (1135-1204)

2.2.2. Development of circadian rhythm

The exact development of the circadian clock in the SCN is unclear. The pioneering brain lesion studies in the 1970s (Moore and Eichler 1972; Stephan and Zucker 1972) showed that severing this single tissue above the optical nerve chiasma critically disrupts circadian rhythms. Due to the invasiveness of such methodologies, most studies have understandably been performed on animals (Reppert and Weaver 2002). Murine studies show that although the SCN seems to be somewhat developed in mid- to late gestation, it is quite immature and hampered by limited synapses, the number of which increases significantly postpartum. Instead the mother's rhythm seems to influence the nascent SCN, with cues like feeding timing and hormones like melatonin and dopamine that cross the placenta (Sumová et al. 2006; Serón-Ferré et al. 2012; Sumová and Čečmanová 2018). Primate and human post-mortem samples indicate that the SCN exists at gestational week 18, but the amount of vasopressin neurons -a subpopulation of the SCN- is not comparable to that of adults until one year postpartum (Rivkees 2004). One study on baboon infants showed that the SCN seems to respond to light at human gestational week 24 (Hao and Rivkees 1999).

In a study of healthy term babies, Joseph et al. (2015) proposed that postnatal development of circadian rhythmicity is a gradual process, with diurnal cortisol secretion being the first to emerge at ~8 weeks after birth, then the maturation of melatonin secretion and sleep efficiency at ~9 weeks, temperature drop during sleep at 10.8 weeks, and maximum peripheral circadian gene expression at 10.9 weeks. The authors suggested that the early cortisol might have an important role in the development of the other processes that follow. Different studies and methods show different results, however. One study has suggested that diurnal cortisol variation is already developed at four weeks (Ivars et al. 2015), while others place the timing at 8 to 12 weeks (Antonini et al. 2000), and older studies suggest an even later timing (Onishi et al. 1983). Some studies place the development of rhythmic melatonin expression at 12 weeks (Kennaway et al. 1996), and some at 6 to 7 weeks (McGraw et al. 1999). Results for the timing of circadian temperature variation are also variable, with some studies arguing for a clear circadian rhythm within one week of birth (McGraw et al. 1999) and some at 6 to 16 weeks (Petersen et al. 1991; Lodemore et al. 1992). Rivkees et al. (2004) suggested that although babies usually do not display consolidated periods of wake and sleep until a month or two postpartum, some difference in night-day-activity has been shown in babies

only one week old. Interpretation of infant rhythmic activity is difficult because newborns live such a connected life to the mother, so disentangling the maternal effects from innate rhythmicity is difficult. After all, during the whole gestation period the child has in a sense functioned as a peripheral circadian clock for the mothers central pacemaker (Serón-Ferré et al. 2012).

To summarise, different key anatomical components seem to develop during early gestation, but true independent functioning emerges postnatally. The large variance in results also indicates that extracting true time points for key developmental phases is complicated, even in healthy term-born subjects.

2.2.3. Development of circadian rhythm in preterm babies

Does preterm birth impact the development of circadian rhythm? Does the process speed up or does it follow the original developmental timetable? As with the studies of term-born babies, the results are variable and sometimes in conflict.

Salivary cortisol. Ivars et al. (2015; 2017) showed that development of salivary cortisol circadian rhythm in preterm babies was dependent on gestational age, not postnatal age, so the process did not speed up. The time point for the development of the rhythm was on average one month corrected age for both preterm (28+3 weeks) and term-born infants.

Melatonin. The development and onset of melatonin rhythmicity seems to be more dependent on neurodevelopmental maturation than environmental cues. This suggests that preterm birth does not speed up the initiation of pineal secretion, but might in fact even delay it if the child was exposed to cerebral insults (Kennaway et al. 1992; Jan et al. 2007).

Temperature. A Brazilian study (Bueno and Menna-Barreto 2016) used wrist thermometers and actigraphs in the NICU to measure circadian temperature onset and movement in three groups of infants: one term and two preterm (28-31 and 32-36 weeks). The study suggested that circadian temperature variation might already function at gestational week 29, so the impact of preterm birth remained unclear.

Sleep-wake. Using actigraphy and parental questionnaires, Guyer et al. (2015) inferred from consolidated sleep periods and lower nocturnal activity that age-corrected circadian rhythmicity in very preterm neonates seemed to emerge earlier than in their term-born counterparts. This corroborated an earlier study (McMillen et al. 1991), which

found that appropriate entrainment to night/day developed after similar exposure to external cues in a preterm (9.8 weeks) and term group (8.7 weeks), but at an earlier postmenstrual age for the preterm group (47.0 vs 48.9 weeks), implying that exposure is more important than neuroanatomical maturation. The opposite is argued by Shimada et al.'s study (1999), however, in which both preterm and term infants displayed diurnal sleep-wake rhythms at 44.8 gestational weeks.

The role of illumination. A limitation to many of the studies is the variable standardisation of lighting in the neonatal wards: some NICUs used constant dim lighting, some constant bright light, and some cycled lighting. A constant dim or near dark lighting might simulate the intrauterine illumination, but it does not simulate the intrauterine experience, however, because although the fetus lives in darkness, it does not live in isolation (Ariagno and Mirmiran 2001). The fetus constantly receives information about the outside world via the mother in a sensory flow of sound, movement, hormones, and nutrients, so arguably cycled light in the NICU might better simulate the actual rhythmic experience in the womb. Cycled light seems to hasten adaptation to a diurnal rhythm after discharge (Rivkees et al. 2004), and a Cochrane review from 2016 (Morag & Ohlsson) found that cycled light seems to shorten length of stay. The review summarizes: "Although results of this review favour the use of cycled light (CL) versus near darkness (ND), and CL versus continuous bright light (CBL), studies published to date preclude a clear conclusion. CL appears preferable to CBL". Cycled lighting was officially recommended in the US in 1997 (American Academy of Pediatrics 1997). At the Children's Hospital in Helsinki, Finland, the habit of covering incubators at night was likely gradually incorporated in the early 1990s (personal correspondence, Prof. Sture Andersson).

2.2.4. Chronotype

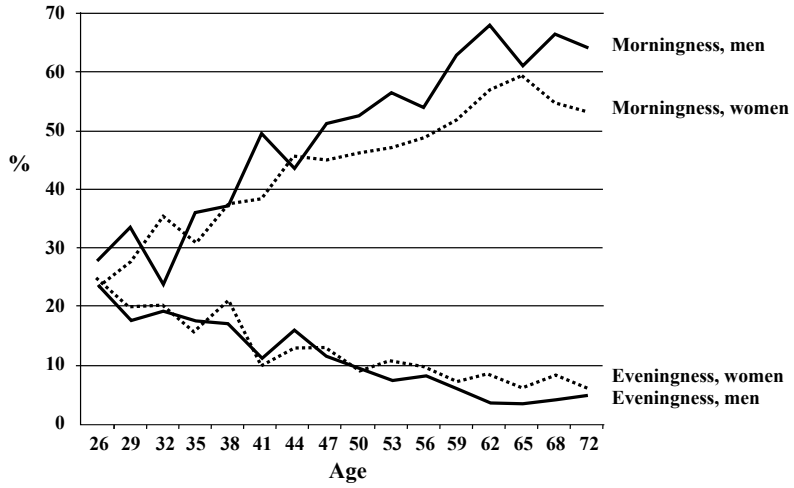
Most people know an early bird; the person who has finished a morning run before others eat breakfast, but then struggles to stay awake for a late evening movie. Most people also know the opposite type, the person who preferably sleeps until noon and returns to bed in the small hours of the morning. These two types are colloquially called 'morning larks' and 'night owls', and they display a trait called chronotype, which can be defined in two ways (Taylor and Hasler 2018; Vetter 2018): firstly chronotype describes the subjective preferred timing for activity and sleep. The preference towards earlier or later times is called 'morningness' and 'eveningness', and questionnaires often classify people as 'morning', 'intermediate', or 'evening' chronotypes (Horne and Östberg 1976). Secondly chronotype describes a person's phase of entrainment, simply put the temporal relationship with the outside world, and can be reported as a continuous variable, e.g. midpoint of sleep (Wirz-Justice 2007). Therefore chronotype is not merely a psychological trait; it aligns well with physiological measures of rhythm, such as core body temperature, melatonin synthesis, and heart rate (Baehr et al. 2000; Griefahn 2002).

Epidemiology. Epidemiological studies have shown that chronotype seems to shift during a person's life (Roenneberg et al. 2007; Randler et al. 2017). As most parents will attest, small children are usually more active in the earlier part of the day, whereas teenagers are more commonly night owls. After adolescence chronotype seems to advance (become earlier) during adulthood, corroborating the finding that seniors are often more active in the morning. This progression seems to be innate, and some authors have suggested that the transition to an earlier chronotype might serve as a marker for adulthood. One study has indicated that this happens on average at 19.5 years for women and 21 for men (Roenneberg et al. 2004), but another study argues that maximal lateness occurs earlier, at 15.7 years for girls and 17.2 in boys (Randler et al. 2017). A sex difference exists in the progression of chronotype, with men usually displaying later chronotypes during adolescence, but after age 50 these differences usually diminish, possibly due to menopause (Roenneberg et al. 2004). The earlier chronotype among seniors might also be a form of survivor bias, caused by the greater mortality among later chronotypes. Basnet et al. (2017) reported findings from 4414 respondents (mean age 51, SD 14 years) of the Finnish FINRISK 2012 study who completed an abbreviated morningness-eveningness questionnaire. A total of 43.8% reported being morning types, 42.7% intermediate types, and 3.5% evening types. In a sense it is not productive to

report aggregated population-level statistics of chronotype prevalence, however, because chronotype is so dependent on age and sex, so stratified, longitudinal data is more useful (Figure 8).

Figure 8. Prevalence of chronotypes by age. With age the prevalence of morningness increases and eveningness decreases.

Modified Figure 1 from Ilona Merikanto, Erkki Kronholm, Markku Peltonen, Tiina Laatikainen, Tuuli Lahti & Timo Partonen (2012) Relation of Chronotype to Sleep Complaints in the General Finnish Population, Chronobiology International, 29:3, 311-317, DOI: 10.3109/07420528.2012.655870. Used with permission from Taylor & Francis, https://www.tandfonline.com/doi/full/10.3109/07420528.2012.655870.



Chronobiology. Chronobiologists use the term 'phase of entrainment' to describe how an oscillating (repeating) phenomenon is temporally related to another under a certain entrainment. *Phase* is just a time point in an oscillation, but the concept *entrainment* requires some unpacking: it describes an adjusting effect on an oscillation. The most studied example of entrainment is how light shifts circadian timing. If a subject is exposed to bright light late in the evening the sleep-wake rhythm is usually *delayed* (shifts later), whereas light early in the morning *advances* (shifts earlier) the rhythm. How strongly light shifts the circadian rhythm is dependent on the *amplitude* (strength), duration, and relative timing of the light impulse, and the effect can be plotted in so called phase response curves (Hilaire et al. 2012). Light is the most potent source of entrainment and in modern societies it is arguably the most pervasive due to the abundance of artificial lighting (Tähkämö et al. 2018). Examples of non-photic entrainment include

exercise (Tahara et al. 2017) and eating schedules (Tahara and Shibata 2018). Sleep-wake rhythm is naturally also influenced by sleep. The traditional two-process model by Borbély (1982) suggests that sleep and wake are regulated by two independent processes, the circadian process (C) and sleep homeostatic process (S), and their interaction determines sleep timing, duration, and quality (see Figure 12, p. 62). In practice, isolating only one variable in this equation is challenging, because humans are continually exposed to different zeitgebers, and different behaviours lead to different exposures. Studies show, however, that individuals with different chronotypes consistently display different phases of entrainment despite living in same conditions. Why is this?

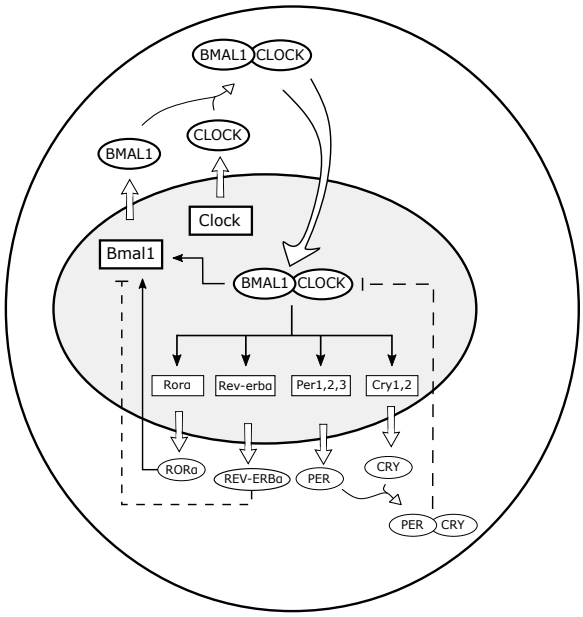
Conceptually, on a chronobiological level, a difference in phase of entrainment might be due to three different things (Roenneberg, Daan, et al. 2003). Firstly, the experience of the input might differ, e.g. if the stimulus is transduced with different efficiency it affects how strongly the oscillation shifts in response to the exposure. Secondly, free-running settings like constant dark reveal that the internal 24h clock ticks at different paces between individuals and is not necessarily exactly 24 hours long. The length of this internal day is called the *period*, or in free-running settings tau (τ). It is often over 24h, and on average longer in men than in women (24h 11min vs 24 h 5 min, Duffy et al. 2011). In idealised settings, a shorter period causes an earlier phase of entrainment, and a longer period causes a later phase of entrainment, and indeed morning chronotypes tend to have shorter periods than evening chronotypes (Duffy et al. 2001). The truth is, however, that the period is malleable, and external lighting conditions can lengthen or shorten it (Scheer et al. 2007). Thirdly, it is possible that even if two individuals experience the same zeitgeber the same way, and have identical periods, that the measured output (e.g. sleep-wake rhythm) is coupled in a different way to the circadian clock, producing different timings.

Behaviour also influences chronotype. Morning larks often experience more solar entrainment because they are up early enough to be exposed to it, and in consequence their rhythms stay early. Night owls might miss the strongest effects of daylight and are thus more weakly entrained, leading to later rhythms. Ecological factors are also important, e.g. urbanised life with less direct sunlight causes inhabitants of larger cities to have later chronotypes (Roenneberg and Merrow 2007). Wright et al. (2013) took eight subjects camping without any artificial light for one week, and found that the natural sunlight exposure significantly advanced melatonin and sleep-wake rhythms, with the largest shifts seen in later chronotypes. Populations living in preindustrial settings also

display much earlier chronotypes, usually waking up before sunrise (Yetish et al. 2015). Not only is the entrainment of sunshine beneficial because it advances later chronotypes, it also delays extremely early chronotypes, so in settings of strong light the distribution of displayed chronotype narrows (Roenneberg, Wirz-Justice, et al. 2003).

Genetics. Chronotype clearly has genetic underpinnings, with twin and family studies showing a broad-sense heritability of 37-54% (Hur et al. 1998; Vink et al. 2001; Koskenvuo et al. 2007; Barclay et al. 2010; Watson et al. 2013; von Schantz et al. 2015), whereas genome-wide association studies have suggested a heritability of 12-21% (Hu et al. 2016; Jones et al. 2016; Lane et al. 2016; Jones et al. 2019). The results indicate that chronotype is a polygenic trait, and that different genes influence the phenotype at different ages (Vink et al. 2001). Also, the heritability seems to differ with age: one study with young adolescents (mean age 12.8 years) showed that heritability of self-reported chronotype was 75%, and that of free-day sleep midpoint was 90% (Inderkum and Tarokh 2018).

Figure 9. Simplified schematics of the molecular circadian clock. The BMAL1-CLOCK heterodimer promotes transcription of BMAL1 in the nucleus, but also activates other genes such as the PER- and CRY family, which in turn repress their own transcription. This positive and negative feedback-loop causes a ~24 h molecular machinery. Solid lines = stimulation, dashed lines = repression. Figure by the author, based on Figure 1 in Zanquetta et al. (2010, CC BY 2.0).



Investigations into specific chronotype-related genes and mechanisms have evolved as the field of genetics itself has evolved. Earlier studies mostly focused on known cogwheels of the circadian machinery (Figure 9), and discovered associations between chronotype and polymorphisms in the genes *CLOCK*, *PER1*, *PER2*, and *PER3* (Kalmbach et al. 2017). Another early approach was to look for culprit genes in familial sleep phase pathologies, in which the chronotype is pathologically out of sync with the environment. Some of these studies implicated mutations in *PER2*, *CSNK1D*, and *CRY2* for being relevant in advanced sleep phase disorder, whereas a mutation in *CRY1* was displayed in a family with delayed sleep phase disorder (von Schantz 2017).

More recently, genetic investigation has simultaneously become more sophisticated, with increasingly accurate phenotyping of circadian rhythmicity, and more blunt, where lesser accuracy is compensated by massive samples sizes. On the sophisticated side, studies have investigated possible genetic couplings between clock genes and bipolar disorder, schizophrenia, depression, anxiety, and addiction (Schuch et al. 2018), and how circadian genetics might mediate disease (Takeda and Maemura 2015). Compared to many molecular processes the circadian clock is quite well defined, which perhaps explains why it has been the first target in the genetic manipulation of monkey embryos: in 2018 (Qiu et al. 2019) a Chinese team utilized CRISPR/Cas9-editing to produce eight *BMAL1*-deficient macaques (*Macaca fascicularis*). Moving on to the massive studies, four large genome-wide association studies supported some previous gene sites, and revealed many new loci (Hu et al. 2016; Jones et al. 2016; Lane et al. 2016; Jones et al. 2019). The three GWAS from 2016 found associations between chronotype and the genes *PER2*, *RGS16*, *FBXL13*, and *AK5* (Kalmbach et al. 2017), and the GWAS from 2019, with an astounding 697,828 individuals, found associations in further 327 loci. This expanding knowledge has allowed the development of polygenic risk scores (Merikanto et al. 2018) and novel methods for determining internal circadian time from blood samples or hair follicles (Akashi et al. 2010; Wittenbrink et al. 2018).

2.2.5. Outcomes of chronotype

Considering that circadian rhythm is so hardwired in our fabric, it is hardly surprising that it impacts health and wellbeing. The following sections will outline some outcomes linked to chronotype and speculate on why and how chronotype might influence health.

Intelligence and education. Some studies have shown that night owls score higher in intelligence tests (Kanazawa and Perina 2009), but these findings are not uncontested (Zerbini and Merrow 2017). The recent GWAS found that morningness was negatively correlated with intelligence (Jones et al. 2019), however, which suggests that although chronotype changes with age, it might have an enduring effect on attributes like intelligence. Other studies have suggested that night owls are more creative (Giampietro and Cavallera 2007). One might assume that the possibly more intelligent and creative mind would facilitate educational achievement, but that is not the case: large meta-analyses show that evening types perform worse in school and at the university (Tonetti et al. 2015). This speaks volumes about how current societal schedules disfavour night owls, and this is most clearly seen in teens. Chronotype changes with age and reaches maximal lateness during late adolescence, so why do we assume that teenagers should fit into the same temporal mould as adults or young children? A Cochrane review (Marx et al. 2017) summarized all studies before February 2016 that investigated the effects of delaying school mornings, and concluded that such interventions seem to increase sleep duration. A recent study measured with actigraphs the effect of delaying school mornings in two subsequent classes of 16-year-olds in 2016-2017, and found that delaying school start by 55 min increased school night sleep duration by 34 min (Dunster et al. 2018). Another study showed that delaying school mornings by 1 hour possibly decreased car crashes of high schoolers by up to 70% (Wahlstrom et al. 2014). A further complication in the educational attainment of night owls is that a later chronotype is quite consistently associated with attention deficit hyperactivity disorder (Coogan and McGowan 2017).

Mental health. Few outcomes related to chronotype have received as much study as depression. Patients suffering from major depressive disorder often display concurrent circadian rhythm disturbances that can predispose a depressive episode, exacerbate current symptoms, or increase treatment resistance. A recent meta-analysis of 36 studies showed that eveningness was related to severity of mood disorder symptoms, albeit the aggregated effect size was small ($z = -0.2$, Au & Reece 2017). Another recent study suggested that the association between chronotype and depression is not necessarily linear

across all chronotype groups, but the link might be restricted to late chronotypes, defined in that study as the one-third of participants with the latest corrected sleep midpoint (Dimitrov et al. 2018). Still on the topic of mood disorders, eveningness is associated with nonremission of depression (Chan et al. 2014), more thoughts of suicide (Rumble et al. 2018), impaired emotion regulation (Watts and Norbury 2017), and more rumination (Antypa et al. 2017). Different chronobiological theories of mood disorders have tried to answer why circadian disruption and depression are interconnected. One example is the model of internal coincidence, which postulates that depression arises when sleep is not synchronised with the internal night. Another model is the social rhythm hypothesis, which suggests that disruption of non-photic zeitgebers such as social rhythms, cause physiological circadian disruptions. Research into the genetic origins of depression and bipolar disease have implicated some clock genes such as *BMAL1*, *Per3*, and *Timeless*, which even further cements the observed clinical association (Zaki et al. 2018). Most beforementioned studies have been cross-sectional, which poses a chicken-and-egg problem: which comes first, depression or eveningness? One of the first longitudinal efforts to investigate this question studied young adolescents during a 48-month period, and the answer seems to be both: previous depression predicted greater eveningness, and eveningness predicted depression (Haraden et al. 2017). Other psychiatric diagnoses have received less attention than depression, but studies also indicate an association between chronotype and anxiety, bipolar, and eating disorders, but no clear association with psychotic disorders has emerged (Kivelä et al. 2018).

Personality & behaviour. Regarding personality and behaviour, some studies show that later chronotypes display more extroversion and impulsivity and lower conscientiousness (Adan et al. 2012; Lipnevich et al. 2017). The link to lower conscientiousness is important, because it might serve as a mediator regarding outcomes like educational achievement and exercise (Hisler et al. 2017; Zerbini and Merrow 2017), but chronotype also seems to be independently associated with lesser self-reported and objectively measured exercise frequency and activity (Wennman et al. 2015; Wong et al. 2015; Hisler et al. 2017). Regarding other unhealthy behaviours, later chronotypes seem to be more prone to addictions, such as to alcohol and narcotics (Kivelä et al. 2018), and epidemiological studies like the UK Biobank report a higher frequency of smoking (Patterson et al. 2016).

Cardiometabolic health. The Finnish national FINRISK studies have repeatedly found an association between eveningness and cardiovascular risk factors, such as

increased blood pressure, diagnosis of hypertension, and cardiac insufficiency (Merikanto, Lahti, Puolijoki, et al. 2013; Basnet et al. 2017; Basnet et al. 2018). In one UK Biobank study with 433,268 subjects, definite evening types displayed greater odds for cardiovascular disease, diabetes, and neurological, endocrine, renal, respiratory, musculoskeletal, gastrointestinal, and psychological disorders (Knutson and von Schantz 2018). The study also found an increased risk in all-cause mortality (HR 1.02) and possibly in cardiovascular mortality (1.04, $p = 0.06$). Epidemiological studies show that evening types more often have type 2 diabetes and metabolic disorders, they display poorer glycemic control if they are diabetic, and they have higher hemoglobin A1c in prediabetic conditions (Merikanto, Lahti, Puolijoki, et al. 2013; Reutrakul et al. 2013; Yu et al. 2015; Anothaisintawee et al. 2017).

Health-related quality of life. Considering that practically all associations related above show unfavourable outcomes for later chronotypes in societal demands, mental health, behaviour, fitness, cardiovascular health, mortality, and endocrine disorders, it is hardly surprising that evening types also report lower health-related quality of life (Suh et al. 2017). The recent GWAS (Jones et al. 2019) also found that morningness was positively correlated with subjective well-being.

2.2.6. Why does chronotype influence health?

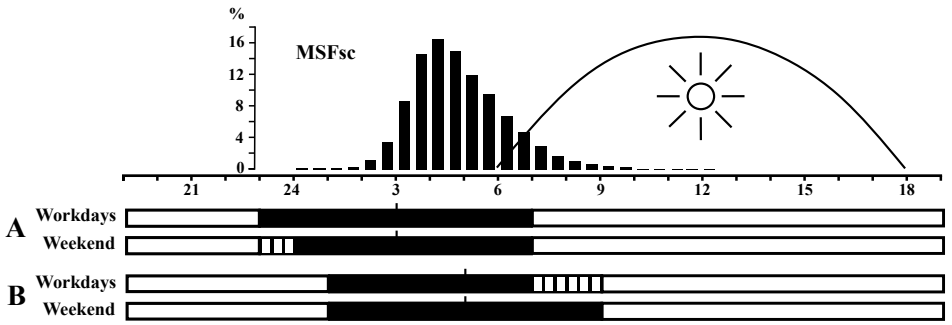
Are the problems caused by sleep deficit? We can conceptually imagine that our lives are governed by different clocks. Relevant thus far have been the solar clock and our internal clock. There exists an additional clock, however, namely the social clock. As a whole our societies do not work for the advantage of evening types (Figure 10): later chronotypes usually accrue sleep deficit during the work week because they are unable to fall asleep in time to get the required rest before the morning alarm goes off. This deficit is usually compensated during the weekend by sleeping in. This phenomenon is called 'Social Jet Lag' (Wittmann et al. 2006) because it resembles living in different time zones during the week. Early chronotypes are not immune to this phenomenon either because they might accrue sleep debt due to late night socializing. As demonstrated in Figure 10, theoretically evening types are prone to accrue sleep deficit due to social jet lag, and this has been supported by clinical studies (Vitale et al. 2015). Insufficient sleep is widely associated with poor health outcomes, so certainly it must play a role in eveningness morbidity.

Figure 10. Social jet lag. Columns display the distribution of sleep-debt-corrected sleep midpoint of 55,000 respondents. Consider the crude examples **A** and **B**, with preferred sleep midpoints at 3 and 5 am and similar 8h sleep need. On work mornings both wake up at 7 am, and both socialize until midnight on weekends. White = wake, black = sleep, stripes = sleep debt.

A is a moderately morning-oriented person, and has no problems getting up at 7 am on workdays, having slept a full night. During weekends A must stay awake an hour longer than usual and is unable to sleep in due to the circadian clock. Therefore, A accrues sleep debt during weekends.

B is a moderately evening-oriented person, and cannot fall asleep before 1 am, but due to work must wake up at 7 am, accruing two hours of sleep debt every workday. B has no problems with late socializing during weekends.

Figure by the author except for the prevalence, which is from Figure 1 in Roenneberg et al. 2007. Epidemiology of the human circadian clock. Sleep Medicine Reviews. Volume 11, issue 6, pages 429-38. Reused with permission of Elsevier, license #4441231189845.



Are the problems caused by circadian misalignment? If activity and sleep do not coincide with the central pacemaker's rhythm, they are in misalignment, e.g. being active during the internal night. This not only applies to those in misalignment due to chronotype, but also to e.g. night shift workers, an estimated 19% of the European work force (eurofound.europa.eu). Epidemiological studies have shown that working night shifts is associated with increased odds for depression (Lee et al. 2017), obesity (Sun et al. 2018), and breast cancer in pre-menopausal women (Cordina-Duverger et al. 2018). But how can we untangle whether the morbidity is caused by circadian misalignment or sleep deficit? Some cross-sectional studies have tried to answer the question by adjusting for self-reported sleep duration e.g. Anothaisintawee et al. (2017) discovered higher HbA1c in later chronotypes also after adjusting for sleep duration, and Merikanto et al. (2015) reported higher odds for depression even when adjusted for the experienced sleep amount. Other studies have subjected participants to 20- or 28-hour days, which are so different from the innate period that humans cannot entrain to them. One of these *forced desynchrony* studies showed that circadian misalignment decreased the hunger-inhibiting hormone leptin, increased glucose and insulin levels, increased mean arterial pressure, and reversed the cortisol rhythm (Scheer et al. 2009). Notably, in 3 out of the 8 healthy participants the circadian misalignment caused postprandial glucose profiles resembling prediabetic states. Circadian misalignment also decreased sleep efficiency, meaning that the impact of sleep deficiency could not be ruled out in this setting either, although the results did survive adjustments. Leproult et al. (2014) came up with a clever study setting to circumvent the issue of sleep loss. The authors compared metabolic outcomes between two groups: one group with stable circadian timing, and the other continually shifted, but they subjected the same amount of sleep deprivation to both groups, verified with polysomnography. They found that circadian misalignment doubled measures of systemic inflammation, and insulin sensitivity dropped by half in the male participants. These findings support the notion that circadian misalignment has an inherent pathological effect, independent of sleep deprivation.

Are the problems caused by behavioural choices? Another reason for adverse outcomes is the link between later chronotype and poorer health-related behaviour. As mentioned earlier, evening types more often tend to be smokers, they consume more alcohol and narcotics, they tend to be more impulsive, and less conscientious. But is the unhealthy behaviour a consequence of coping with circadian misalignment, or is the circadian misalignment due to unhealthy behaviour? One study has suggested that some

psychological outcomes of late chronotype are mediated by smoking and alcohol consumption (Wittmann et al. 2010), but nevertheless the causal determination between chronotype and behavioural choices needs to be examined in prospective studies.

Are the problems caused by common genetic origin of disease? This is the frontier of chronotype research, and understandably a definite answer has yet to emerge. Most of these investigations have been psychiatric, and studies to date imply that "the CLOCK gene exerts important influence" on conditions such as autism spectrum disorder, schizophrenia, ADHD, major depressive disorder, bipolar disorder, anxiety disorder, and substance use disorder (Schuch et al. 2018). The most recent GWAS found that chronotype was associated with psychiatric outcomes, in particular that morningness was negatively correlated with schizophrenia, depressive symptoms, and major depressive disorder (Jones et al. 2019). Mendelian randomization analyses investigated causation and suggested that increased self-reported morningness was causally associated with reduced liability for schizophrenia, major depressive disorder, and depressive symptoms, whereas the opposite direction was not supported. Importantly, the authors "found no evidence for a causal effect of morningness on type 2 diabetes, BMI or insulin levels", which might indicate that pathways like circadian misalignment might better explain this aspect of night owl morbidity.

Summary. The evidence is overwhelming that a later chronotype is linked to undesirable outcomes, such as higher mortality, morbidity, and poorer quality of life. The exact mechanisms are unclear, and the emerging data indicate that the causal links are complex and many-layered; genetics determine chronobiological attributes that in turn are entrained by behavioural choices, and the individual with this nuanced phenotype is then forced into our current temporal societal structures, to the apparent detriment of night owls.

2.2.7. Preterm birth and chronotype

Few studies have specifically set out to study chronotype in preterm subjects, so some outcomes highlighted here were originally reported in passing (Table 1). Also, given that the methodologies for studying chronotype vary and have evolved significantly, it is difficult to synthesize the relevant studies, even if they measured the same phenomenon. The participant age ranges from neonates to young adults, and the methodology ranges from parental questionnaires to polysomnography (PSG), and none of the studies investigated the effect of post-term birth. Mentioned weeks and weights are means, unless noted otherwise.

Neonates and toddlers. The youngest subjects in a preterm circadian-rhythm study were ~12 months old (Asaka and Takada 2010). The study used actigraphs to monitor the sleep-wake cycle of 14 VLBW children and 14 controls. The VLBW children displayed 24 min earlier sleep onset and 42 min earlier offset during night-time. They displayed 19 min less nocturnal sleep, but similar total sleep duration. Caravale et al. (2017) asked mothers of 51 preterm and 57 term-born two-year-olds to complete the adapted Sleep Disturbance Scale for Children and Brief Infant Sleep Questionnaire. No differences emerged regarding sleep patterns or sleep durations, e.g. bedtimes were 21:34 vs 21:44. Five children were born extremely preterm, 17 very preterm, and 29 moderate-to-late preterm.

Children. A series of one-night, at-home, PSG studies with salivary cortisol analysis performed in a cohort of VP children in the University Children's Hospital in Basel, Switzerland reported varying results. One study (Perkinson-Gloor et al. 2015) studied the children (52 VP and 50 controls) at around 8 years, and did not discover a difference in parent-reported awakening times (06:42 vs 06:48, $F = 1.3$, $p = 0.26$). The morning cortisol profiles did not differ between groups, but the preterms displayed a faster falling evening cortisol profile. A later study (Maurer et al. 2016) with 58 VP and 85 term-born children, at age 9.5 years, found that PSG-measured sleep onset was 13 minutes earlier in the VP group (21:11 vs 21:24, $p = 0.013$), and sleep duration was 0.1 hours longer ($p = 0.066$). Stangenes et al. (2017) queried weekday sleep habits of parents to 11-year-old extremely preterm/ELBW subjects in a national longitudinal study and controls recruited from another study. Compared to 556 term-born children, the 231 preterm children reported 0.4h earlier bedtime (24 min, 20:54 vs 21:18, $p < 0.05$). Rise

Table 1. Case-control studies reporting quantitative or qualitative chronotype of subjects born preterm.

Author, year	Grade of prematurity	n, preterm/control	Age (SD) of preterms	Method (duration)	Outcome
Caravale et al. 2017	EP, VP, moderate and late	5/17/29/57	20.9 (4.1) months	SDSC, BISQ	Non-significant ~10 min earlier bedtime.
Stangenes et al. 2017	EP <28wks or ELBW <1000g	231/556	11 years	Questionnaire about weekdays	24 min earlier bedtime.
Maurer et al. 2016	VP <32 weeks	58/85	~9.5 (1.4) years	Single night, in-home PSG	13 min earlier sleep onset time.
Perkinson-Gloor et al. 2015	VP <32 weeks	52/50	~8.2 (1.3) years	Single night, in-home PSG	Non-significant 6 min earlier awakening time.
Hibbs et al. 2014	<37 weeks	217/284	17.8 (0.4) years	Actigraphy (instructions 5-7 days)	24 min earlier midsleep on weekends.
		146/190		Self-report questionnaire	37 min earlier midsleep on weekends.
Strang-Karlsson et al. 2010	VLBW <1500g	91/93	~24.9 (2.0) years	MEQ	Morningness propensity (2.8 points difference).
Asaka & Takada 2010	VLBW <1500g	14/14	13.3 (2.1) months	Actigraphy (instructions ~7 days)	24 min earlier sleep onset, 42 min earlier offset.
Strang-Karlsson et al. 2008	VLBW <1500g	89/78	22.4 (2.0) years	Actigraphy (range 2-9)	36 min earlier bed time.
		164		BNSQ	24 min earlier awakening on weekends.
Natale et al. 2005	<37 weeks	55/210	13 years	junior MEQ	Morningness propensity (3.7).
		40/318		junior CS	Morningness propensity (1.8)

Method and Outcome show the most central method and finding regarding chronotype, prioritising measures of midsleep from free days.

BISQ, Brief Infant Sleep Questionnaire; BNSQ, Basic Nordic Sleep Questionnaire; CS, Composite Scale; ELBW, extremely low birth weight; EP, extremely preterm; MEQ, Morningness-Eveningness Questionnaire; SD, standard deviation; SDSC, Sleep Disturbance Scale for Children; VLBW, very low birth weight; VP, Very Preterm.

time was similar, sleep latency was 6.2 min longer, and time in bed was 0.4h longer, of which actual sleep duration was 0.3h longer.

Adolescents. Natale et al. (2005) measured subjective chronotype of preterm 13-year-olds and controls with the Junior Morningness-Eveningness Questionnaire (n = 55, 210) and the Junior Composite Scale (n = 40, 318). The preterm group (34.8 weeks), contained more 'morning types' (45.5% vs 22.9%, $p < 0.005$ and 25.0% vs 14.5%, $p = 0.08$), and the mean scores from both questionnaires indicated a stronger tendency towards morningness in the preterm group (57.3 vs 53.6, $p < 0.001$ and 29.3 vs 27.4, $p < 0.05$). Hibbs et al. (2014) performed an extensive sleep analysis in the Cleveland Children's Sleep and Health Study using overnight PSG, self-reported sleeping times, actigraphy, and sleep hygiene questionnaires. A total of 217 preterm adolescents (1514 g, 31 weeks) and 284 term-born controls participated at a mean age of 17.8 years. Not only is this study noteworthy due to the comprehensive methods, it is also the first preterm study to report sleep midpoint, an improved proxy for circadian timing (see 2.4). The preterm adolescents displayed an earlier circadian timing in both self-report and actigraphy. Self-report: 23 min earlier weekday midsleep ($p = 0.03$), 37 min earlier weekend midsleep ($p < 0.001$). Actigraphy: 22 min earlier weekday midsleep ($p = 0.02$), 24 min earlier weekend midsleep ($p = 0.04$).

Adults. Moving on to older subjects, Strang-Karlsson et al. studied young adults in the HeSVA cohort using both MEQ and actigraphy. In the actigraphy study, the 89 VLBW young adults (~22.5 years) displayed 36 min earlier bedtime than the 78 controls (23:59 vs 00:35, p = .019), and the preterm group reported earlier wake-up time in the Basic Nordic Sleep Questionnaire (workdays 30 min, free days 24 min, Strang-Karlsson et al. 2007). In a follow-up study 91 VLBW young adults (~25 years) reported stronger tendency towards morningness than the controls (2.8 points higher Morningness-Eveningness Score, 95% CI 0.1 to 5.5, p = 0.04, Cohen's d = 0.3, Strang-Karlsson et al. 2010).

Limitations. There are many limitations in these studies. Only one (Hibbs et al. 2014) reported actigraphy-measured sleep midpoint, and only one study actually used PSG to measure sleep timing (Maurer et al. 2016). The practice of not reporting sleep midpoint is also a limitation (see 2.4). One study reporting an earlier bedtime also reported significantly longer sleep duration (Stangenes et al. 2017), and in another there was a similar trend (Maurer et al. 2016), which complicates the interpretation. Several of the actigraphy studies do not mention the actual amount of registered nights, and instead describe instructions (5-7 nights in Hibbs et al., "approximately seven" in Asaka and Takada). Other limitations worth considering is that one study used unvalidated sleep questionnaires, that also differed slightly in phrasing between preterm and term-born subjects (Stangenes et al. 2017). Further, parental report of sleep schedule is usually quite reliable in small children (Asaka and Takada 2011), but might be more questionable at adolescence.

Summary. Although the outcomes vary in these studies, some features can be discerned. Albeit two studies did not find a significant difference in chronotype, the remaining seven did, and they all point to the same direction, namely earlier awakenings and/or earlier sleep onset. None of the studies discovered a later rhythm, and in fact, the two studies that did not discover a statistically different timing (Perkinson-Gloor et al. 2015; Caravale et al. 2017), did nonetheless both report earlier awakenings and bedtimes in the preterm group. The Cohen's d for both the earlier awakening time in Perkinson-Gloor et al. and the earlier bedtime in Caravale et al. was ~0.23. The weight of the studies therefore suggest an earlier chronotype among preterm subjects, both with objective and subjective measurements.

2.2.8. Could early experience program circadian rhythm?

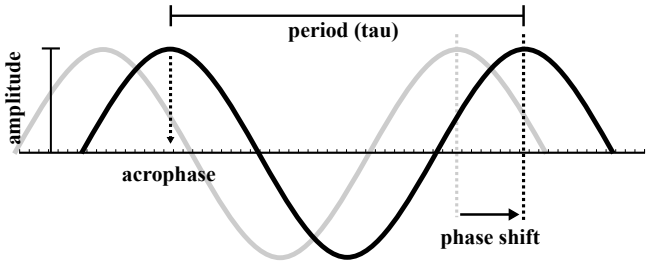
Spontaneous premature birth is an elusive phenomenon. The underlying reasons often remain unknown, and possible investigations are usually *post hoc* in human studies. Animal studies are not equivalent substitutes, but they provide an opportunity to perform exposure studies, with much fewer variables. This author is unaware of studies investigating the circadian rhythm of prematurely born animals, but some studies have first simulated poor intrauterine conditions and then investigated the offspring's circadian rhythms. Understandably none of the following conditions are a substitute for premature birth, and many important postnatal exposures such as brain haemorrhage and stress related to intensive care are not addressed, but these animal studies might provide insight, nonetheless.

> *''All models are wrong but some are useful''*
>
> *George Box (1919-2013)*

Hypoxia. Joseph et al. (2002) placed pregnant rats in a hypoxic chamber (10% O_2) between days 5-20 of gestation (23-91% of term). The authors then compared wheel-running activity between the adult offspring of 7 hypoxic and 6 control rats in a 12h light/12h dark regime. Rats being nocturnal animals, the control group initiated running activity 83 min after lights-off, but the hypoxic rats began their activity 4 min *before* lights-off. No difference emerged in cessation of activity or in total activity duration, but overall the hypoxic rats were less active. The light-dark regime also involved one abrupt delay of 6 hours, to see how well the rats entrained to a new rhythm. The hypoxic rats needed significantly more time (9 vs 6 days) to resynchronise. The hypoxic rats also showed a blunted delay of rhythm when exposed to a sudden bright light in a constant dark setting. Furthermore, they displayed sustained elevation of corticosterone in response to stress. All rats had similar periods of circadian activity, i.e. the internal day was equally long.

Maternal stress. Koehl et al. (1997; 1999) subjected pregnant rats to stress during the last week of pregnancy. The stress constituted of being exposed to bright light several times a day inside a transparent cylinder. The authors then investigated the corticosterone rhythm of the adult offspring and found that rats from the exposed group displayed an elevation of cortisol levels four hours before lights-off, whereas the control group displayed similar levels at lights-off.

Figure 11. Brief glossary of chronobiological concepts, following definitions at www.chronobiology.ch/glossary/. Figure by the author.



Acrophase: Phase angle corresponding to maximal value of the rhythmic parameter**.**
Amplitude: The measure of one half of the extent of the rhythmic change.
Period: Time after which a defined phase of the oscillation re-occurs.
Phase: Instantaneous state of an oscillation within a period.
Phase angle: Position of a parameter value relative to the period.
Phase shift: Displacement of an oscillation either earlier (advancement) or later (delay).

Malnutrition. Several studies have used protein restriction during pregnancy to cause fetal malnutrition. The most recent (Crossland et al. 2017) did not discover a different timing in wheel-running of adult male rats whose gestation was marked by limited maternal protein intake, nor did the study find changes in hypothalamic circadian gene expression. Orozco-Solís et al. (2011) studied circadian gene expression in adult rats deprived of protein during gestation and lactation, and found that the exposure had long-lasting effects on the timing of core clock gene expression in the hypothalamus, but not in the periphery. The effects were complex, with some acrophases showing advancement, and some delays. Sutton et al. (2010) noted that fetal malnutrition in mice increased sensitivity towards diet-induced obesity, which was preceded by abnormal daily rhythms, arrhythmic expression of circadian oscillator genes, and reduced peripheral expression of Rev-erbα. Durán et al. (2005) investigated spontaneous locomotor activity in male rats whose mothers were protein-deprived before mating and during pregnancy. The study found similar total levels of activity in exposed and control rats, but the activity duration was shorter in the exposed group, and importantly the acrophases were different: malnourished rats began their activity about 50 min before lighting change, whilst controls began theirs about one hour after.

Alcohol. A study from 2007 showed that consuming an alcohol-containing liquid diet (35% of calories) during days 14 to 20 of gestation (64-91% of term) had the following effects on offspring circadian rhythm: earlier rise of core body temperature at ages 4 and 18 months, no difference in diurnal variation in heart rate, and the rise of

corticosterone in anticipation of the active period was dampened (Handa et al. 2007). A Texas-based group has produced several papers on this topic: in four papers they studied the effects neonatal alcohol exposure had on rats, which regarding brain maturation timing equals the third human trimester. The group found that exposed rats adapted faster to a 6-hour advance in the light-dark regime, overall they displayed more variable and earlier initiation of wheel-running activity, and they also had a shorter period of activity in free-running setting (Farnell et al. 2004; Allen, West, et al. 2005; Allen, Farnell, et al. 2005; Farnell et al. 2008). In the 2008 study, the authors investigated the circadian pattern of core clock gene expression and found phase-advanced *Per2* expression in the cerebellum and liver, and dampened *Cry1* expression in the SCN. The group has also found decreased SCN neuronal density (Farnell et al. 2004). Not all findings are unchallenged, however, e.g. Sei et al. (2003) found that phase shift response was dampened instead of increased.

Chronodisruption. Whereas the previously mentioned exposures might simulate poor or even toxic intrauterine environments, chronodisruption can feasibly serve as a model for the non-circadian stimuli a prematurely born baby experiences in early postnatal life, such as the variable noise and light in a NICU. Many studies have investigated the role of perinatal lighting, and most seem to describe long-term effects on later circadian functioning, e.g. in behaviour (Canal-Corretger et al. 2000; Canal-Corretger et al. 2001; Smith and Canal 2009), protein levels in the SCN (Smith and Canal 2009; Brooks et al. 2011), and changes in astrocyte organization (Canal et al. 2009). Brooks et al.'s (2014) thorough study investigated the effects of postnatal lighting on many levels: continuous lighting after birth did not damage the retina, nor damage retinal function to a serious degree, but it did shorten the period significantly. In a later continuous dark setting no differences were apparent, however, implying that without photic zeitgeber the circadian clock behaves similarly. The authors did not find a significant difference in the magnitude of phase shift to a light pulse. The authors also studied expression of *Per2::LUC* in both central and peripheral organs, and found an advanced rhythm in the spleen. Ciarlegio et al. (2011) set out to study if different day lengths impacted expression of core clock genes for developing mice. The authors found that mice exposed to long days (16:8h) during weaning displayed narrower waveform of *Per1*::GFP expression on the single-cell level, and the rhythmic period was shorter than in short-day mice (8:16h). This was also apparent in behaviour: in free-running conditions the long-day mice had shorter internal periods. Smith & Canal (2009) found that, in mice

reared in constant light, the levels of SCN-produced proteins arginine-vasopressin and vasointestinal polypeptide were decreased, but they did not discover a different phase of entrainment, nor a different period between groups. Canal-Corretger et al. (2001) did not find that postnatal lighting produced a difference in entrainment to darkness onset, there was no difference in phase shift after a light pulse in later constant darkness, and there was no difference in free running period.

Melatonin deficiency. During pregnancy the developing child is in a sense a peripheral oscillator to the mother's central pacemaker, and it receives circadian signals in many forms, such as maternal melatonin, which readily crosses the placenta (Serón-Ferré et al. 2012). As mentioned in 2.2.3., the development and onset of melatonin rhythmicity seems more dependent on neurodevelopmental maturation than environmental cues. This implies that the 2-4 month-long melatonin deficiency that term infants experience, is even longer if the child is born prematurely, not to mention with possible neurological insults that even further seems to postpone initiation of pineal secretion (Kennaway et al. 1992; Jan et al. 2007). Thus, it is possible that a melatonin deficiency could influence later circadian rhythmicity. At least one rodent study has shown that mice deprived of maternal melatonin, by excising the mothers pineal gland during pregnancy, displayed desynchronized drinking behaviour, and a wider distribution of the internal period, which in turn was corrected with melatonin treatment (Bellavia et al. 2006).

Summary. The caveat from the beginning bears repeating; none of these exposures are a substitute for human premature birth. Nonetheless, it is interesting that all these insults seem to impact chronobiology, and quite often, regardless of the exposure, the insult seems to cause an earlier rhythm or shorter period. So, based on these studies it is certainly possible that early adverse exposures could impact circadian rhythmicity also in humans.

2.3. Sleep

"If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made."

> Allan Rechtschaffen
> University of Chicago Sleep Laboratory Smithsonian,
> November 1978

Humans spend a third of their lives lying prone in a non-responsive, apparently catatonic state, oblivious of and utterly helpless against the outside world, all while internally experiencing wild hallucinations and psychotic thinking. We pursue this state of abandon every night, and should it persistently escape our grasp our minds and bodies are left in ruin. It is curious that although sleep dominates so much of our lives and is so critical for our health and wellbeing, it remains such a mystery. The subsequent chapters of this thesis will outline current knowledge regarding what sleep is, why we sleep, what happens when we sleep, and critically what happens when we don't.

2.3.1. What is sleep?

These elements often appear in definitions for sleep: it is a rapidly reversible state of decreased response to external stimuli where the sleeper remains still in species-typical locations and postures, and this state shows homeostatic rebound after deficit (Miyazaki et al. 2017). This definition is useful because it separates sleep from other resembling states, e.g. quiet rest is a rapidly reversible state of stillness but response to external stimuli is unimpaired, and a patient in general anaesthesia is still and unresponsive but the condition is not rapidly reversible. It is crucial to point out that these are behavioural manifestations for a phenomenon whose core function is unknown, and the definition might change dramatically once we discover what sleep actually is. Therefore the question "*what is sleep*" is connected to the question "*why do we sleep*".

One way of investigating what sleep does has been to restrict it. These sleep deprivation studies have indicated that sleep, especially slow wave activity, is essential in e.g. metabolic regulation, memory consolidation and formation, brain plasticity, thermoregulation, and immune and endocrine functioning (Anafi et al. 2019). Based on these findings, some hypotheses have emerged to explain why we sleep. The metabolic dysregulation related to sleep deprivation has suggested that sleep is essential for *energy conservation*, because continuous peak performance is seldom required. This hypothesis does not account for Rapid Eye Movement (REM)-sleep, however, during which energy expenditure increases. Another hypothesis is that sleep is a period for *cellular recovery*, when transmitter vesicles and macronutrients are replenished (Mignot 2008). One hypothesis which links energy homeostasis with the decreased cognitive abilities of sleep deprivation is the *synapse homeostasis* hypothesis (Tononi and Cirelli 2014). It postulates that when the brain encounters conspicuous coincidences, relevant synapses strengthen. And because continuous neuronal firing would be very expensive metabolically (the brain accounts for 25% of the body's energy expenditure) a resting period is required. During this rest weaker connections fall into oblivion and stronger ones prevail, so that unnecessary information is forgot, which is paramount for survival.

Sleep deprivation studies have an inherent problem, however. They describe how sleep restriction causes systems to break down, but compensatory sleep and regular sleep seem to be different things (Seidner et al. 2015; Dubowy et al. 2016). Therefore, this method might not investigate what function regular sleep has. A high-level approach to investigate sleep is to study non-human subjects (Anafi et al. 2019). Every animal that

has received in-depth study, from the roundworm *C.Elegans* to the elephant, has been shown to sleep according to some, most, or all behavioural requirements. But returning to the earlier point; if the core function of sleep is unknown, why do we assume that sleep in all life forms should resemble that of humans? Well-known exceptions to traditional appearances are bottlenose dolphins and some migratory birds that seem to sleep with one brain hemisphere at a time. Other exceptions are new-born whales and their mothers, who after parturition apparently ignore sleeping for a month without need for compensation (Cirelli and Tononi 2008).

Evolutionary biology has provided other insights about sleep, such as its deep history and what components are essential. Sleep between widely different species display similar molecular reactions to e.g. dopamine, melatonin, and caffeine, so the rules of parsimony suggest a common ancestor who slept, rather than assuming that similar mechanisms arose independently in different phyla. The most distant evolutionary cousin to show elements of sleep, in this case diurnal activity and homeostatic rebound after rest disruption, is the upside-down jellyfish in the phylum Cnidaria. The last common ancestor of Cnidaria and its sister lineage bilateria, which encompasses most known animals, lived over 600 million years ago, so sleep could be at least equally ancient (Anafi et al. 2019). The upside-down jellyfish is also interesting because it lacks a central nervous system. If it sleeps, then the core function of sleep is unlikely brain-specific. Even more provocative is the finding that sleep might also be regulated by non-neuronal tissue: a research team utilised BMAL1-knock-out mice to investigate how restoration of BMAL1 in different tissues affected sleep, and found that restoration of BMAL1 in brain tissue did not correct the sleep phenotype, but restoration in muscle tissue did (Ehlen et al. 2017).

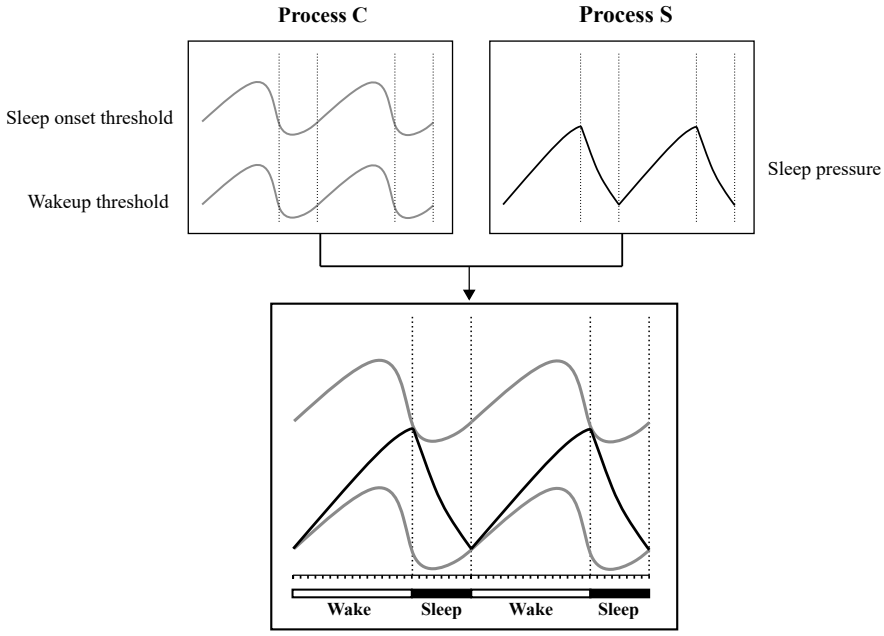
Anafi et al. (2019) suggest that a rudimentary temporal organization of metabolic processes in the early organisms might have allowed other processes to become optimised for some part of the cycle. Studies on simple organisms show that such alternating states could conserve energy, temporally segregate incompatible reactions, allow better coordination of resources, and display higher energetic efficiency. It is quite possible that this process, given a chance to elaborate for millions of years in a world of diurnal light and dark, could ultimately have formed what we call sleep.

2.3.2. What happens when we sleep?

Far from being a passive state of consciousness, akin to shutting off a machine, sleep is an active, cyclical process. Shortly after the advent of the electroencephalogram, Loomis et al. showed in the 1930s that cortical activity seems to display a rhythmical, repeating pattern during sleep, or to quote the paper: '...certain hours of sleep show many "spontaneous" bursts of waves, while other hours show relatively few' (Loomis et al. 1935). Loomis et al. also described the electroencephalogram recording shapes of "spindles", "trains", and "saw-tooth waves"; familiar terms even to modern-day sleep researchers. In 1953, Kleitman and Aserinsky noted conspicuous eye-movement during certain phases of sleep, possibly related to dreaming (Aserinsky and Kleitman 1953). This state of "paradoxical sleep", as coined by Michel Jouvet (Arnulf et al. 2018), is today known as Rapid Eye Movement (REM) sleep. It was paradoxical because the brain activity and eye movements suggested that the obviously sleeping subject was awake. Today sleep is categorized as either REM sleep or non-REM (NREM) sleep, which is further subdivided into three levels of depth. During night, sleepers undergo repeated cycles of NREM and REM sleep with possible momentary wakefulness between cycles. NREM sleep is often more prominent during early night, and REM sleep in later. Studies have shown that both types of sleep are essential, and deprivation of either will lead to rebounding. Dreaming is most pronounced and vivid during REM sleep but is also present in NREM sleep.

On a neurobiological level, sleep- and wake-promoting systems activate and regulate sleep. The sleep-promoting system seems to be largely GABAergic nuclei in the preoptic area, brainstem, and lateral hypothalamus. The wake-promoting regions seem to be largely cholinergic and monoaminergic, and they receive input from the hypothalamic hypocretin/orexin system (Schwartz and Kilduff 2015). An example of their activity is that loss of wake-promoting orexin-producing neurons causes narcolepsy. Different models have attempted to explain what regulates the sleep-wake cycle and one of the most enduring is the two-process model proposed by Borbély (Figure 12, Borbély 1982; Borbély et al. 2016). Other models have included the three-oscillator model by Winfree et al., which suggests that the sleep-wake rhythm is generated by three oscillators: one for sleep, one for wake, and one for circadian oscillation (Kawato et al. 1982).

Figure 12. The two-process model suggests that sleep and wake are regulated by two independent mechanisms: the circadian process (C) and sleep homeostatic process (S). C regulates the circadian proneness to fall asleep, whereas S describes the accumulation or dissipation of sleep pressure by wake and sleep (Borbély 1982). The interaction of the two processes determines sleep timing, duration, and quality. Recent studies have questioned whether the two processes are truly independent, because some cross-talk and genetic overlap seem to exist (Franken & Dijk 2009; Borbély et al. 2016). Figure by the author, based on the work of Borbély.



Genetic investigations of sleep regulation are complex, and studies to date have not yet discovered a similar molecular framework for sleep as exists for circadian clocks, and a complication is that some genes influence both. The heritability of characteristics such as sleep duration and quality seems to be 17-44% (Partinen et al. 1983; Heath et al. 1990; Klei et al. 2005; Gottlieb et al. 2007). A GWAS with European populations revealed a variant in *ABCC9* that may explain ~5% of the variance in sleep duration (Allebrandt et al. 2013), and one of the UK Biobank studies found three loci associated with sleep duration: one near *PAX8* and two on *VRK2* (Jones et al. 2016). The recent UK Biobank GWAS found further 76 loci associated with sleep duration (Dashti et al. 2019). Examples of genes influencing both the circadian system and sleep homeostasis are *PER3* and *DEC2* (Zhang and Fu 2018).

2.3.3. What happens when we do not sleep?

Although the minimum sleep duration recommendation for adults is seven hours (Hirshkowitz et al. 2015; Watson et al. 2015), recent self-reported data from the US show that one third of adults sleep six hours or less (Sheehan et al. 2018). Although the survey showed a 15% increase in prevalence of short sleep during 2004-17, claiming clear trends is not straightforward. Systematic reviews of data from the 1960s onward in developed countries have suggested, apart from some exceptions, that long sleep is becoming more usual, and short sleep is becoming less common (Bin et al. 2012; Bin et al. 2013; Matricciani et al. 2017). To gain a quasi-historical perspective, an actigraphy study of three current preindustrial societies in Tanzania, Namibia, and Bolivia showed that the sleep period duration (time between onset and offset) ranged from 6.9 to 8.5 hours (Yetish et al. 2015); numbers similar to current recommendations. There seem to exist natural short sleepers who suffer no adverse consequences from sleeping six hours or less, as evidenced by genetic studies in families where carriers of mutations in *DEC2* sleep on average 6.25 hours without noticeable impairments (He et al. 2009; Pellegrino et al. 2014). The prevalence of natural short sleepers is unknown and likely quite rare.

Anecdotes about successful people thriving despite little sleep are plentiful, and an illuminating case is Napoléon Bonaparte, "the Nightmare of Europe". He is wrongly attributed this prescription for sleep hours: "Six for a man, seven for a woman, and eight for a fool" (Roenneberg 2012; Stanley), and he supposedly slept from midnight to 2 am, and then again from 5 to 7 am, a sum of four hours. His private secretary described a more relatable emperor in his memoirs, however (de Bourrienne and Phipps 1829):

> *"…, his flatterers, probably under the idea that sleep is incompatible with greatness, have evinced an equal disregard of truth in speaking of his night-watching. Bonaparte made others watch, but he himself slept, and slept well. His orders were that I should call him every morning at seven. I was therefore the first to enter his chamber; but very frequently when I awoke him he would turn himself, and say, "Ah, Bourrienne! let me lie a little longer." When there was no very pressing business I did not disturb him again till eight o'clock. He in general slept seven hours out of the twenty-four, besides taking a short nap in the afternoon."*
>
> *Memoirs of Napoleon Bonaparte, Complete*
> *by Louis Antoine Fauvelet de Bourrienne*

So, what happens if we sleep too little? Some of the most explicit studies show that continuously sleep-deprived rats, flies, and cockroaches will develop multi-organ failure and die (Rechtschaffen and Bergmann 2002; Shaw et al. 2002; Stephenson et al. 2007). A human example is familial fatal insomnia, a hereditary prion disease like Creutzfeld-Jacobs, which causes a sleep deprivation condition that usually leads to death in 8-72 months (Montagna and Lugaresi 2002). Volunteers for sleep deprivation have managed to stay awake for astonishingly long periods: a widely known case is Randy Gardner who - under scientific scrutiny- stayed awake for 264 hours (11 days, Ross 1965). Sleeping less than six hours is robustly associated with poor health outcomes. A comprehensive review and meta-analysis of 153 studies showed that short sleep (<6 h) is associated with a 12% increase in mortality (RR 1.12), 37% increase for diabetes, 17% for hypertension, 16% for cardiovascular disease, 26% for coronary heart disease, and 38% for obesity (Itani et al. 2017). A meta-regression from the same year (Liu et al. 2017), which included 40 prospective cohort studies, found that total 24h sleep duration mortality followed a J-shaped curve, with minimal mortality at 7 hours of sleep, and increased mortality in both shorter and longer sleep. Regarding mental health, another meta-analysis of seven prospective studies showed that both short and long sleep were associated with increased risk for depression (Zhai et al. 2015). The sleep-deprived brain displays many changed characteristics: decreased attention, impaired working memory, increased risk- and reward-related approach behaviours, reduced accuracy in emotion discrimination and expression, and impaired learning and memory formation (Abel et al. 2013; Krause et al. 2017). One aspect that is quite neglected in the massive sleep duration studies is the importance of sleep quality. For example, the adverse findings related to long sleep could be interpreted differently if the sleep was of low efficiency (Chaput et al. 2018).

2.3.4. Preterm birth and sleep

What do we know about sleep duration and quality among preterms? Some studies highlighted here and in Table 2 are more thoroughly introduced in 2.2.7 and will only receive brief description here. Mentioned weeks and weights are means, unless noted otherwise.

Neonates and toddlers. Huang et al. (2014) queried parents of 191 six-month-old preterms (32 weeks, 1647 grams) and 68 term-born infants with the Brief Infant Sleep Questionnaire. The preterm infants displayed longer night- and day-time sleep durations (54 and 92 min longer), and more night awakenings. The study included actigraphy and PSG-assessments, but their function was to validate the Chinese questionnaire, and were not reported. Asaka & Takada's (2010) actigraphy study of 13-month-old VLBW toddlers reported 19 min shorter nocturnal sleep duration, but no difference in total sleep duration, sleep efficiency, or wake after sleep onset. Gössel-Symank et al.'s (2004) actigraphy study with 17 preterm children (29.3 weeks, 1160 grams) and 8 controls at 20 months of age found that the day and night-time rest period in the preterm group was 40 and 45 min shorter, and sleep was more restless. Caravale et al. (2017), using the Sleep Disturbance Scale for Children and the Brief Infant Sleep Questionnaire, reported that 51 preterm two-year-olds did not differ from 57 term-born controls regarding sleep duration, but they displayed more nocturnal sleep problems.

Children. Iglowstein et al. (2006) performed a longitudinal study of sleep behaviour in 130 preterm and 75 term-born children, in the form of 11-15 structured interviews between birth and age ten. The median for gestational weeks was 34.1 (range 27.1-36.8), including 30 very preterm subjects. The authors did not discover significant differences in sleep duration or nocturnal awakenings. The Basel-based series of one-night, at-home, PSG studies performed in a cohort of very preterm children showed variable outcomes. At age 8.2 (SD 1.3) Hagmann-von Arx et al. (2014) reported no group differences in sleep duration or efficiency, but more nocturnal awakenings. At the same age, Perkinson-Gloor et al. (2015) did not discover differences in total sleep time or sleep efficiency, but noted more nocturnal awakenings and stage 2 sleep, and less slow wave sleep. At age 9.5 (SD 1.4) Maurer et al. (2016) noted 6 min longer sleep duration ($p = 0.066$), but no difference in sleep efficiency. Another team of researchers investigated 5-to-12-year-old preterms with or without fetal growth restriction ($n = 17$ and 15) and compared sleep to 20 term-born controls using one-night PSG (Yiallourou et al. 2017).

They found that “prematurity and FGR [fetal growth restriction] were associated with altered sleep macro- and micro-architecture measures indicative of reduced sleep quantity and quality in childhood”, e.g. 45-64 min less total sleep time in preterm children born appropriate for gestational age, compared to growth-restricted preterm children and term-born children. The large Norwegian study of extremely preterm/ELBW 11-year-olds by Stangenes et al. (2017) found that parent-reported sleep duration was ~18 min longer in the preterm group, and that the prevalence of sleep problems increased with the degree of neurodevelopmental disabilities, but even unimpaired preterm children reported more sleep problems than controls.

Adolescents. Hibbs et al. (2014) have likely published the only case-control results of sleep duration and quality in preterm teenagers, aged 17.8 ±0.4 years. PSG, actigraphy, self-reported sleeping times, and sleep hygiene questionnaires did not indicate a difference in sleep duration, but the PSG indicated fewer nocturnal arousals among the preterm adolescents, and they reported feeling more rested and alert in the morning.

Adults. Before the thesis studies, possibly only Strang-Karlsson et al. (2007) had investigated sleep in a cohort of adult VLBW preterms (n = 89). Compared to term-born controls (n = 78), the study found no significant differences in sleep duration or efficiency when measured with actigraphy or the Basic Nordic Sleep Questionnaire.

Sleep-disordered breathing. An important possible mediator of poor sleep quality is sleep-disordered breathing, which ranges from primary snoring to obstructive sleep apnoea syndrome. Although preterms often display problems with airway maturation, the link between sleep-disordered breathing and prematurity is not always clear, as described in the textbook *Respiratory Outcomes in Preterm Infants* (Hibbs and Muhlebach 2017). During infancy preterm babies are at increased risk for Spontaneous Infant Death Syndrome and periodic breathing. Data is conflicting regarding preschool age, but during middle childhood the evidence somewhat consistently indicate an increased risk for sleep-disordered breathing. Clinical studies have not found a convincing association between obstructive sleep apnoea syndrome and prematurity in adolescence, and the only clinical study on adults showed that after multivariate adjustments chronic snoring was 2.2 times more likely among VLBW young adults (Paavonen et al. 2007). A recent registry study from Sweden investigated the incidence of sleep apnoea and adenotonsillar hypertrophy in subjects born 1973-2014, and found that these diagnoses were strongly associated with lower gestational age in early childhood

and adulthood but the association was much weaker in late childhood/adolescence (Crump et al. 2019).

Summary. Studies that have investigated sleep duration and quality among prematurely born subjects vary in results and do not provide a simple answer. During infancy and toddlerhood, some studies report longer sleep durations, other shorter, but the majority suggest poorer sleep quality. During childhood, studies indicate both longer and shorter sleep, and the majority indicate no difference in sleep efficiency, but nocturnal awakenings seem to be more frequent. During adolescence no difference in sleep duration is apparent, but preterm teens subjectively report feeling more rested after sleep, and PSG indicates fewer nocturnal awakenings. During adulthood no difference in sleep duration or quality has emerged. These studies have used varying methodologies, so a simple aggregation of the outcomes is not feasible, but one interpretation is that potential differences in sleep duration and quality seem to diminish with age.

Table 2. Case-control studies reporting sleep duration or efficiency of subjects born preterm.

Author, year	Grade of prematurity	n, preterm/control	Age (SD) of preterms	Method	Outcome
Yiallourou et al. 2017	<37 weeks	30 (17 FGR)/20	9 (0.5-0.6) years	Overnight PSG	Altered sleep architecture indicative of reduced sleep quantity and quality.
Caravale et al. 2017	EP <28, VP <32, moderate and late 32-36 weeks	5/17/29/57	20.9 (4.1) months	SDSC, BISQ	No differences in nocturnal or daytime sleep durations. More medical sleep problems, but less behavioral sleep problems.
Stangenes et al. 2017	EP <28 weeks, ELBW <1000g	231/556	11 years	Questionnaire about weekdays	Sleep duration 0.3 h longer, more sleep problems.
Maurer et al. 2016	VP <32 weeks	58/85	~9.5 (1.4) years	Single night, in-home PSG	0.1 h longer sleep duration ($p = 0.066$). No difference in sleep efficiency.
Perkinson-Gloor et al. 2015	VP <32 weeks	52/50	~8.2 (1.3) years	Single night, in-home PSG	No mean differences in total sleep time or efficiency, but more nocturnal awakenings.
Hagmann-von Arx et al. 2014	VP <32 weeks	58/55	8.2-8.3 (1.3)	Single night, in-home PSG	No difference in total sleep time or sleep efficiency, but more nocturnal awakenings.
Hibbs et al. 2014	<37 weeks	217/284	17.8 (0.4) years	Actigraphy, PSG, and questionnaire	No difference in sleep duration, and the PSG discovered fewer arousals. The questionnaire indicated feeling more rested and alert in the morning, and less sleepy and fatigued.
Huang et al. 2014	<37 weeks	191/68	6 months	Chinese BISQ	Longer nocturnal and daytime sleep duration, more night awakenings and sleep problems.
Asaka & Takada 2010	VLBW <1500g	14/14	13.3 (2.1) months	Actigraphy	19 min less sleep duration during nighttime, no difference in total sleep duration. No difference in WASO or sleep efficiency.
Strang-Karlsson et al. 2008	VLBW <1500g	89/78	22.4 (2.0) years	Actigraphy	No significant difference in sleep duration, efficiency, or fragmentation index.
Iglowstein et al. 2006	<37 weeks	130/75	birth to 10 years	Structured interview, longitudinal study	No significant differences in sleep duration, night wakings, bedtime resistance, or sleep-onset difficulties.
Gössel-Symank 2004	<34 weeks	17/8	20 months	Actigraphy	Shorter daytime rest duration and less restful nighttime sleep.

BISQ, Brief Infant Sleep Questionnaire; BNSQ, Basic Nordic Sleep Questionnaire; FGR, fetal growth restriction; ELBW, extremely low birth weight; EP, extremely preterm; PSG, polysomnography; SD, standard deviation; SDSC, Sleep Disturbance Scale for Children; VLBW, very low birth weight; VP, Very Preterm; WASO, wake after sleep onset.

2.4. How to measure chronotype and sleep

"In physical science a first essential step in the direction of learning any subject is to find principles of numerical reckoning and methods for practicably measuring some quality connected with it. I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of *science*, whatever the matter may be."

William Thomson, 1st Baron Kelvin
Lecture on "Electrical Units of Measurement" (Thomson 1889)

As Lord Kelvin so eloquently expressed, any effort to truly understand the science of a phenomenon requires that it can be expressed in numbers. This thesis chapter will therefore delve into some historical and technical aspects of chronotype and sleep quantification, focusing on the validity of the thesis methods.

2.4.1. Origins of chronobiological research

Although the field of chronobiology has gained attention during the last decades, as evidenced by a Nobel prize in 2017 for work in describing the circadian clock (Nobel Foundation 2017), the field has quite venerable roots. The first study of circadian rhythms was performed by the French scientist Jean-Jacques d'Ortous de Mairan (1678-1771), who in 1729 noticed that the foliage of the *Mimosa pudica* opened and closed in a diurnal manner despite being placed in the constant darkness of a closet (de Mairan 1729). Arguably the first person to specifically study chronotype was the eminent psychiatrist Emil Wilhelm Magnus Georg Kraepelin (1856-1926), who at the turn of the 20th century had his doctoral students measure how time of day affected e.g. physical capacity and number addition. They found that people displayed different aptitudes at different times, or as his student Axel Oehm put it: "Prof. Kraepelin was convinced that physical capacity was subject to regular fluctuations depending on the time of day and that those fluctuations were different with different individuals" (Becker et al. 2016). Another notable historical milestone was when Heinrich Lampert (1898-1981) coined the now ubiquitous labels "larks" and "owls" for different chronotypes (Lampert 1939). In modern times, the term chronotype is commonly defined as either 1) a temporal preference for activity and sleep or 2) a phase of entrainment, that is, the temporal relationship of a circadian output to an external oscillator, most often the day-night cycle (Taylor and Hasler 2018; Vetter 2018). The connection between the two descriptions is robust, as evidenced by the agreement between questionnaires and objective measurements like dim-light melatonin onset (DLMO) and core body temperature (Horne and Östberg 1977; Duffy et al. 1999; Baehr et al. 2000; Duffy et al. 2001; Kantermann et al. 2015).

2.4.2. Measurement of chronotype with questionnaires – focus on MEQ

Attempts to measure the subjective temporal preference for activity and sleep have understandably taken the format of questionnaires. This aspect of chronotype, also called circadian or diurnal preference, or qualitative chronotype (Roenneberg, Wirz-Justice, et al. 2003), was first systematically measured with the Morningness-Eveningness Questionnaire (MEQ) by Horne & Östberg in the 1970s (Horne and Östberg 1976). They validated the MEQ to body temperature profiles of young adults, and it also corresponds well to other circadian physiological markers like melatonin and cortisol (Horne and

Östberg 1977; Baehr et al. 2000; Bailey and Heitkemper 2001; Duffy et al. 2001). The questionnaire consists of 19 questions that query respondents about subjective preferences, hypothetical scenarios, and approximate clock times for different activities, such as peak mental and physical performance. The questions produce a Morningness-Eveningness Score (range 16-86) with higher values indicating morningness. Based on the score, subjects can fall into three "types": morning, intermediate, or evening. Division into five types is also possible: definite morning, moderate morning, intermediate, moderate evening, and definite evening. Epidemiological studies often employ an abbreviated version called the Reduced Morningness-Eveningness Questionnaire (Adan and Almirall 1991), which with only five questions correlates to the MEQ in the range of 0.69-0.95 (Adan et al. 2012; Montaruli et al. 2017). The MEQ is the most widely used questionnaire for determining circadian preference, but it has also received critique. For example, the original validation population was young (18-32 years) and chronotype changes with age, so using the MEQ in other age groups and cultures has required different cut-off points (Levandovski et al. 2013).

Other questionnaires worth mentioning are the Composite Scale for Morningness, which utilizes 13 Likert-type questions about subjective preferences (Smith et al. 1989), and the Munich Chronotype Questionnaire (MCTQ, Roenneberg et al. 2007). The MCTQ is a relatively recent addition to chronotype questionnaires, and it is different because it queries phase of entrainment, not subjective preference. With questions like "I actually get ready to fall asleep at ____o'clock" the questionnaire provides measures of sleep timing such as bedtime, midsleep, and awakening time. The midsleep for free days is more informative than for workdays because the sleep window is usually restricted by work hours. As mentioned in the description of social jet lag (2.2.6.), especially evening types accrue sleep deficit during the workweek, which manifests itself as longer sleep during free days and a later sleep midpoint. To account for this Roenneberg et al. proposed the derivative midsleep on free days corrected for sleep debt MSFsc, calculated as:

> "MSFsc = MSF - 0.5*(SDF - (5*SDW + 2*SDF)/7) where SDF is sleep duration on free days and SDW is sleep duration on work days. (5*SDW + 2*SDF)/7 represents the average weekly sleep duration or need" (Roenneberg et al. 2004).

The MSFsc has proved useful for epidemiological and genetic studies that benefit from having a single quantifiable measure for chronotype, and it correlates well with both MEQ (Zavada et al. 2005) and melatonin onset (Kantermann et al. 2015). It is important

to stress, however, that the MEQ and MCTQ measure different aspects of chronotype: the MEQ measures it as a trait, whereas the MCTQ measures it as a state (Putilov 2017). Because MSFsc is an output that is transferable to other methodologies, it has found traction in studies that use objective methods for determining sleep timing, such as Studies I-III in this thesis. The MCTQ also asks about use of alarm clocks and the amount of time spent outdoors etc. The questionnaire has received some critique because arguably habitual sleep timing is a result of a complex interaction between environmental zeitgebers, the circadian clock, and sleep homeostasis (Putilov 2017), so MSFsc might not accurately describe phase angle differences.

2.4.3. Measurement of circadian rhythms

Objective measurement of chronotype requires investigation of some reliable output of central pacemaker activity. Although gene expression analysis is becoming a viable method for determining circadian phase (Wittenbrink et al. 2018), the gold standard is still dim-light melatonin onset (DLMO, Klerman et al. 2002). The SCN does not excrete melatonin, but it regulates its release in the pituitary gland based on light stimulus, so that melatonin levels usually start to rise ~2-3h before habitual sleep time (Burgess et al. 2003). The illumination must be dim because light suppresses melatonin release. If two individuals are subjected to identical schedules and entrainment, and the timing of DLMO differs, they have different phases of entrainment; their circadian clocks align differently to the same zeitgeber, and therefore display different chronotypes. Other possible biological outputs are cortisol and core body temperature, but e.g. the latter is easily masked by external temperature, humidity, posture, and sleep (Wirz-Justice 2007). Although DLMO is the current gold standard, it is not the be-all and end-all for determining chronotype, which is a complex phenotype with strong behavioural drives, e.g. the estimated contributions of DLMO on sleep timing difference between morning and evening types might be only 34-49% (Paine and Gander 2016). Also, studies have shown that different chronotypes sleep at different times relative to the DLMO, possibly due to social constraints; evening types wake up at an earlier circadian time than do morning types (Duffy et al. 1999; Baehr et al. 2000; Mongrain et al. 2004). Furthermore, measurement of DLMO, cortisol, and core body temperature often require sleep labs and the capacity for chemical analysis. These methods are therefore labour intensive and costly, which is why other methodologies have gained prominence, such as examining

behavioural rhythms. Sleep-wake rhythms are not direct measures of the circadian clock because they might be masked by behaviour, but they are a useful proxy. Computed sleep midpoint from self-reports display good correlation with DLMO (r = 0.54-0.89, Martin and Eastman 2002; Burgess et al. 2003; Kitamura et al. 2014), but the wide range (4h in Kantermann et al. 2015) restricts its use as a diagnostic tool for treatments. These correlations between sleep midpoint and DLMO are based on self-reports and not objective measurements like actigraphy, but e.g. MCTQ and actigraphy show strong correlation (MSFsc r = 0.73, Santisteban et al. 2018).

2.4.4. Measurement of sleep and chronotype – focus on actigraphy

For almost a century, polysomnography (PSG) has reigned supreme in the study of sleep. PSG utilizes at least three different modes for this purpose: the electroencephalogram measures electrical brain activity, the electromyogram measures muscle activity, and electrooculograms measure eye movement. With these instruments sleep is categorised in sleep stages (see 2.3.2). Polysomnography requires trained staff and expensive equipment, so large scale studies are not feasible, and although sleep logs and questionnaires are valuable self-report tools, studies have shown that they are less reliable than objective measurements (Matthews et al. 2018). Other less laborious objective methods have entered the field during the last decades, one of which is actigraphy. Actigraphs are accelerometers that resemble wristwatches, usually worn on the non-dominant wrist although the choice of wrist does not seem to matter (Driller et al. 2017). Different technologies such as piezoelectric or microelectromechanical systems allow movement detection and the device stores the data as activity counts. The device often has an “event button”, which the subject presses at determined times, e.g. when going to bed or taking a shower. This shows up on the recording and helps identify sleep periods. Based on the activity counts, a software algorithm scores each time unit (“epoch”) as either wake or sleep, with sensitivity and specificity depending on the used settings and epoch lengths. Sleep progresses in cycles, and we are often momentarily awake between cycles, but do not remember it. Therefore, sleep duration can be divided into the self-explanatory measures “actual sleep” and “wake after sleep onset”. The proportion of sleep duration that is spent actually asleep can be expressed as a percentage, called sleep efficiency. Actigraphy is therefore useful for longitudinal assessment of crude sleep and sleep-wake timing, especially if sleep diaries are used in conjunction.

In many respects actigraphy cannot rival PSG, but its minimal invasiveness, good validity, and ease of use allow objective measurement of sleep in home settings. Actigraphs show good construct validity in healthy subjects: an "overall agreement rate of 72.1–96.5% between ACTG [actigraphy] and PSG, a sensitivity range of 86.5–98.7% and a specificity range of 27.7–67.1%" (Van De Water et al. 2011). The two methods do not examine exactly the same thing, however, because they start classifying sleep at different points on the sleep onset spectrum. Actigraphs begin classifying sleep after immobility, whereas electroencephalogram sleep stage 1 was originally validated against decreased muscle tone (dropping hand-held objects). This is one reason why a 100% agreement cannot be expected between the two methods (Tryon 2004). Even if actigraphs tend to misclassify quiescent wakefulness as sleep, as expected in insomniac patients, the recent American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment (Smith et al. 2018) deemed that compared to PSG "actigraphy can be reliably used to provide an objective assessment of TST [total sleep time] for the purpose of making clinical care decisions". They concluded the same for objective measurement of sleep latency, but not for wake after sleep onset and sleep efficiency. Therefore, actigraphy can reliably be used in sleep research if the inherent working principles are kept in mind. In fact, actigraphs are currently unrivalled in objective measurement of sleep-wake rhythms in non-laboratory settings, because they provide reliable longitudinal data about sleep timing, which displays high night-to-night variability. Currently the International Classification of Sleep Disorders recommends that diagnoses of circadian rhythm sleep-wake disorders should be actigraphy-based when possible (Auger et al. 2015), which highlights the method's authority in measuring sleep-wake rhythms.

The recommended recording duration has changed over the years: in practice parameters from 2003 (Littner et al.) three nights were deemed sufficient, in 2007 van Someren et al. suggested that over seven nights was required for reliable interdaily stability estimates, and Rowe et al. showed in 2008 a satisfactory consistency in variable means regardless if measured for 3, 7, or 14 days, but longer durations were superior for measuring variability (Rowe et al. 2008). A recent study on bipolar patients showed that 21 nights of recording reached >95% agreement rate between actigraphy-derived eveningness (sleep midpoint after 4:15 am in >75% of nights) and self-reported eveningness, but the generalizability of the findings is unclear (Gershon et al. 2018).

2.5. Health-related quality of life

"What is most challenging about being born premature is my inability to connect with my early life. It is like waking up in a world where everyone else has experienced war except yourself and there is no evidence of the aftermath. Others can connect with the memories, the trauma, and the anxiety. But all I see is the present and the future."

> Rishi Kapur, adult preterm survivor, birth weight 860 grams.
> Quote from 'Preemie Voices - Young men and women born very prematurely describe their lives, challenges and achievements.' p. 7. (Saigal 2014)

For millennia the good life has been a focus for philosophers and sages, and modern medicine recognizes that a treatment's success is not necessarily measured with laboratory tests or X-rays, but in how the treatment aids us in our search for happiness and satisfaction. Disease and injury might impede this pursuit, but not necessarily, neither does the absence of disease guarantee a life with content and meaning. This last chapter of the review will briefly describe what health-related quality of life is, how there has been confusion in what is measured, and how adult preterm survivors feel about their existence today.

2.5.1. Conceptual framework

On the 22nd of July 1946 representatives from 61 nations signed the constitution for the World Health Organization (WHO 1947), which opens as follows:

> "The States parties to this Constitution declare, in conformity with the Charter of the United Nations, that the following principles are basic to the happiness, harmonious relations and security of all peoples:
>
> Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity…"
>
> Constitution of the World Health Organization, 1947

This constitution is a milestone in modern history and has directed international global health progress for seven decades. The wording of the quoted passage has influenced particularly quality of life (QoL) research, but not necessarily by inducing clarity. Including the term 'well-being' in the definition for health has generated confusion about what QoL is and what health is (Post 2014), and to an extent this confusion still remains. The first use of the term health-related quality of life (HRQoL) was in the 1980s, when it was proposed as a subset of QoL specifically pertaining to the health domain (Torrance 1987). Many questionnaires associated with HRQoL, such as the SF36, actually query health states, which further complicates matters. Therefore, at times the literature uses interchangeably the terms QoL, HRQoL, health status, health, and perceived health. The increased differentiation between these terms is important, because in a way they represent the evolution of medicine; having been the physician's tools for objective measurement of the patient, these questionnaires have become platforms for the patients to subjectively express their health and wellbeing. Herein lie insights of modern medical ethics, namely, why do we treat patients? When we save prematurely born babies on the verge of viability, how should we measure success? Traditionally this has been with rates of mortality and morbidity, but the medical community is increasingly using QoL as a metric of success. The physician and the patient might not share the same opinion regarding what is a problem or not, and indeed studies have indicated that even severely disabled subjects report surprisingly good QoL, giving rise to the term 'disability paradox' (Albrecht and Devlieger 1999).

2.5.2. Preterm birth and health-related quality of life at adult age

Before Study IV, at least 23 studies have described the quality of life of adults born preterm, presented briefly in Table 3. This thesis section refrains from describing each study in detail but will attempt to narratively condense the gist of methods, outcomes, and themes, with the caveat that this will be the author's interpretation.

Types of studies. The majority of the studies are well-defined case-control cohorts from Western Europe, the Nordic countries, Canada, and New Zealand. A notable exception is the Dutch Project On Preterm and Small for gestational age infants (POPS), which does not have a control group, but has provided valuable data on longitudinal change.

Preterm population. The majority of the studies have focused on survivors of very (n = 10) or extremely (n = 7) preterm births, most often defined by birth weight. An exception is the study by Lund et al. (2012), which also included term-born SGA subjects.

Participant age. The McMaster ELBW cohort has reported QoL outcomes on the oldest preterm subjects to date; in the 2016 study the participants were 29-36 years old (Saigal et al. 2016). Publications with longitudinal data became more frequent from 2013 onwards and they have often reported changes from adolescence to adulthood.

Neurosensory impairments (NSI). Most studies have reported the frequencies of NSI and performed separate subgroup analyses. Adequate reporting is important because for some research settings exclusion of impaired subjects allows more accurate investigation of the inherent effects of prematurity. Similar exclusions are problematic in QoL research because reporting an injury's effect on QoL is arguably misleading if those most injured are left out.

Instruments. The most common instrument has been the Short Form Health Survey (n = 12), but more recently the Health Utilities Index (n = 6) has also become more widely used. Most studies have measured HRQoL instead of 'pure' QoL, meaning that quality of life has been assessed based on objective assessments of e.g. functioning, and physical and mental health.

Outcomes and trends. A short summation of the previously published studies is that some studies show a difference in QoL while others do not. If there is a difference, the preterm group is worse off, apart from some exceptions (Dalziel et al. 2007; Natalucci et al. 2013), and common detriments often relate to mental health and physical

Table 3. Studies reporting (Health-related) Quality of life of adult subjects born preterm.

Author, year	Grade of prematurity	n, preterm/control	Age	NSI	QoL questionnaire	Outcome
Husby et al. 2016	VLBW <1500g	35/37	20->23	10	SF36	Lower scores in physical and mental component summaries and most domains, no difference after exclusion of NSI.
Saigal et al. 2016	ELBW <1000g	153/137	12-16-> 22-26-> 29-36	37	HUI3	Subjects had meaningfully poorer HRQoL from early teens to mid thirties. Subjects with NSI appear to display substantially lower HRQL at all ages.
Baumann et al. 2016	VP <32 weeks, VLBW <1500g	190/201	13->26	Yes	HUI3	HRQoL was worse at both timepoints, and did not change when entering adulthood in self-reports.
Båtsvik et al. 2015	EP <28 weeks, ELBW <1000g	46/46	17->24	9	SF36, CHQ-CF 87	Disability-free subjects had lower scores on social functioning, role-emotional and mental health. Severly disabled scored lower on physical functioning.
Vederhus et al. 2015	EP <28 weeks, ELBW <1000g	31/29	10 -> 18	7	CHQ-CF87, YSR	Similar overall HRQoL, but lower self-esteem (girls) and better role/social emotional and self-esteem (boys). More withdrawal, anxiety and depression (girls).
van Lunenburg et al. 2013	VP <32 weeks, VLBW <1500g	705 -> 314*	19->28	137	HUI3, LHS, WHOQoL-BREF	No important changes in the transition to adulthood, but psychological and emotional problems stand out.
Darlow et al. 2013	VLBW <1500g	230/69	22-23	58	SF36v2	No differences on physical or mental component scores or on measures of perceived overall functioning, self-esteem, or life satisfaction.
Roberts et al. 2013	EP <28 weeks, ELBW <1000g	194/148	18	~15	HUI 3, SF36	Similar overall QoL and health status, but lower physical functioning and dexterity-related QoL.
Ulrich et al. 2013	32 to 36 weeks	69/304	32		Questionnaire	No difference in self-rated general health, health problems, or contentment in daily life.
Beaudoin et al. 2013	<37 weeks	234/149	20	Yes	SF36v2	HRQoL was similar between preterms without prematurity-related respiratory diagnoses and controls.
Natalucci et al. 2013	ELBW <1000g	55	23	2	SF36	Worse scores on social functioning and mental component summary. Better on bodily pain, general health, and physical component summary.
Lund et al. 2012	VLBW <1500g, term SGA	43/55/74	20	3	SF36	Lower scores for mental health. Term SGA had lower scores for mental health, social functioning, and emotional role.

Verrips et al. 2012	VP <32 weeks, VLBW <1500g	684*	14->19	36	HUI3	No important group level changes, but considerable changes in individual attributes.
Baumgardt et al. 2012	<37 weeks, <1250g	52/75	~23	1	SF36	No overall difference, but lower physical functioning in males.
Odberg & Elgen 2011	LBW <2000g	134/135	~19	No	CHQ-CF87	Lower self-esteem and more challenging family cohesion.
Gäddlin et al. 2009	VLBW <1500g	76/68	20	15	SF36	No difference in mean scores. Handicapped scored lower on physical functioning and physical health.
Saigal et al. 2007	ELBW <1000g	142/133	23	40	SF36	Lower scores on mental health (all) and physical functioning (males). Poorer self-rated health (all and males). No differences if impaired were excluded.
Dalziel et al. 2007	<37 weeks, median 34 weeks	126/66	31	No	SF36	Higher levels of satisfaction in 3/8 domains: bodily pain, general health perception, and social functioning.
Saigal et al. 2006	ELBW <1000g	143/130	23	38	HUI2, standard gamble	Similar HRQoL in mean utility scores.
Cooke et al. 2004	VLBW <1500g	79/71	19-22		SF36	Similar QoL, but lower physical functioning (whole group and males), and lower general health perception (males).
Dinesen & Greisen 2001	VLBW <1500g, LBW <2300g	79/110/69	~17-20	19	Aggernaes QoL model	Poorer objective, but similar subjective QoL in VLBW subjects without handicaps. Handicapped reported lower objective and subjective QoL.
Tideman et al. 2001	<35 weeks	39/23	19	Yes	VAS 100	Subjects did not differ in QoL or self esteem.
Bjerager et al. 1995	VLBW <1500g	85/85	18-20	19	Aggernaes QoL model	Preterm subjects without handicaps had fully comparable QoL with controls, but handicapped subjects dispalyed poorer objective and subjective QoL.

*No control group due to study design. CHQ-CF87, Child form 87; HRQoL, Helath-related Quality of Life; HUI, Health Utilities Index; LHS, London Handicap Scale; QoL, Quality of Life; VAS, Visual Analog Scale; WHOQoL-BREF, WHO Quality of Life instrument, short edition; YSR, Youth Self-Report.

functioning. A longer summation reveals interesting results, primarily regarding subgroups and changes over time. Firstly, separate analyses of NSI-subjects have shown that they quite consistently score lower HRQoL, often in domains of physical health (Bjerager et al. 1995; Dinesen and Greisen 2001; Gäddlin et al. 2009; Båtsvik et al. 2015; Saigal et al. 2016). If analyses first include and then exclude NSI, possible differences in HRQoL between preterms and controls have usually attenuated (Saigal et al. 2007; Husby et al. 2016). Secondly, male and female preterms tend to report differences in different areas of HRQoL: compared to controls, female preterms score poorer in domains of mood and internalisation (Vederhus et al. 2015), and preterm men score poorer in physical functioning (Cooke 2004; Saigal et al. 2007; Baumgardt et al. 2012). Thirdly, only one study has separately investigated the effect of relative birth weight: Lund et al. (2012) showed that SGA subjects scored poorer in mental health, social functioning, and emotional role. Fourthly, there might be a time trend in the results; older studies have tended to show no group-level detriment or negative longitudinal change in impairment-free preterms (Bjerager et al. 1995; Tideman et al. 2001; Saigal et al. 2006; Dalziel et al. 2007; Gäddlin et al. 2009; Baumgardt et al. 2012; Verrips et al. 2012; Beaudoin et al. 2013; Darlow et al. 2013; van Lunenburg et al. 2013; Ulrich et al. 2013), whereas the most recent studies have uniformly reported poorer outcomes (Båtsvik et al. 2015; Baumann et al. 2016; Husby et al. 2016; Saigal et al. 2016), also after exclusion of impaired subjects (Båtsvik et al. 2015; Saigal et al. 2016).

Summary. Is preterm birth related to poorer HRQoL at adult age? The results from these 23 studies are not uniform, so this author submits that instead of trying to force a yes/no answer out of a complex phenomenon, there is room for nuance, and this is most apparent in subgroup analyses. Preterm subjects with NSI constitute a distinct population because they bear the brunt of the morbidity, and at times women and men born preterm view their vulnerabilities differently. Also, the study on term-born SGA subjects revealed that other metrics than gestational age and birth weight are also influential, which implies that analysis by intrauterine growth restriction could prove informative. More recent studies show poorer HRQoL as the preterms grow older and the methodologies improve.

3. AIMS OF THE STUDY

The aim of this thesis was to answer the following questions:

1. Is a very low birth weight (<1500 grams) preterm birth associated with chronotype, sleep duration, or sleep quality at adult age? (Study I & II)

2. Is preterm birth from the whole gestation range (<37 weeks) associated with chronotype, sleep duration, or sleep quality at adult age? (Study III)

3. Is a very low birth weight (<1500 grams) preterm birth associated with poorer health-related quality of life at adult age? (Study IV)

4. METHODS

This chapter will first present the source cohorts, then describe how chronotype, sleep and HRQoL were measured, followed by technical aspects like statistical methods, power calculations, and ethical considerations. Four cohorts and five clinical examinations provided the study population, so great descriptive granularity is not feasible. Instead this chapter will present the methods and subjects in general terms, and the results chapter will present the most central, harmonized findings of the thesis. Specialist readers will therefore at times be directed to the original publications for more detailed information.

4.1. Study subjects

This thesis contains results from four different, but sometimes overlapping case-control cohorts. This section provides a brief overview of these cohorts along with flowcharts (Figure 13 and 14) to clarify their relationships with the studies.

Helsinki Study of VLBW Adults (HeSVA). HeSVA is a birth cohort of VLBW adults born in the Helsinki area (Hovi et al. 2007). The original cohort consisted of 335 VLBW children treated in the NICU of the Children's Hospital at Helsinki University Central Hospital 1978-85. In 2003, 255 (76%) subjects of the original cohort still lived in the greater Helsinki area, and they received invitation to participate in a clinical study. The comparison group consisted of 314 subjects: the next term-born, same-sex, non-SGA singleton born in the same hospital as each VLBW subject. Of the invited, 166 VLBW subjects (65.1%) and 172 controls (54.8%) agreed to participate. These subjects have supplied data in two follow-up studies: #1 in 2004-05 and #2 in 2007-08, at the mean ages of 22.5 and 25 years. **Study IV** describes the HRQoL of 335 participants (163 VLBW, 172 controls) who completed the 15D questionnaire in follow-up #1. The 15D score was not available for one VLBW subject with over three missing answers. **Study I** describes the chronotype and sleep of 75 participants (40 VLBW, 35 controls) who provided actigraphy data in follow-up #2.

Adults born preterm sibling study. This new study compares VLBW adults to their siblings born at term, and it consists partly of participants from previous clinical studies, but mostly new recruits, however. The recruiters initially contacted HeSVA and ESTER Preterm Birth Study VLBW subjects whom records indicated having a sibling

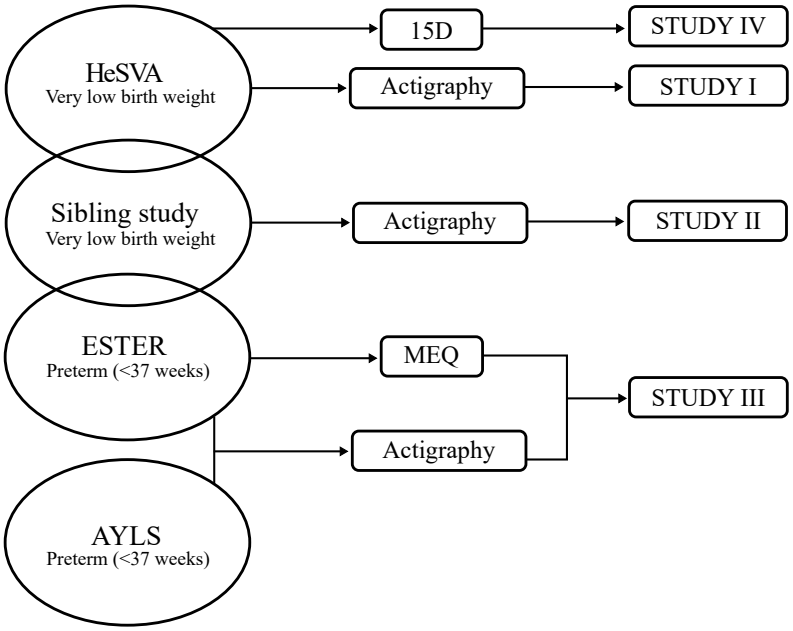
over 18 years, and if willing to participate, the subjects attempted to recruit their sibling. After recruitments from HeSVA and ESTER, the Finnish Medical Birth Register identified potential VLBW subjects with an appropriate sibling from all births in Uusimaa, Varsinais-Suomi, and Northern Häme/Pirkanmaa between 1.1.1987-30.9.1990. Physicians from the birth hospitals recruited VLBW subjects from this pool, for a final total of 79 VLBW-sibling pairs: 22 from HeSVA, 6 from ESTER, and 51 via the birth register. The siblings were of the same sex as the VLBW index, with less than 10 years age difference, and born at term from complication-free pregnancies. In 2014-17, at a mean age of 29.9 years, the subjects underwent extensive testing, such as questionnaire batteries, actigraphy recording, glucose tolerance and fitness tests, X-ray absorptiometry and MRI, and they provided biopsies from muscle and abdominal fat. **Study II** describes the chronotype and sleep of 123 subjects (63 VLBW, 60 controls, 53 whole pairs) who provided valid actigraphy data.

ESTER Preterm Birth Study and Arvo Ylppö Longitudinal Study. ESTER Preterm Birth Study and Arvo Ylppö Longitudinal Study are cohorts with subjects from the whole preterm range, classified as late preterm (34 to <37 weeks) and "early preterm" (<34 weeks) subjects. The subjects of ESTER (Ennenaikainen syntymä, raskaus ja lapsen terveys aikuisiässä, Sipola-Leppänen et al. 2014) came from two sources: 1) the Northern Finland Birth Cohort 1986 (49.8%) born in 1985–86, and 2) a cohort of subjects born 1987–89 (50.2%) in the same area, identified via the Finnish Medical Birth Register. A total of 753 subjects, 38% of the 1980 invited, participated in a clinical study performed in 2009-11, at the mean age of 23.3 years. **Study III** describes MEQ results of 688 (138 early preterm, 221 late preterm, 329 controls) participants in ESTER.

The Arvo Ylppö Longitudinal Study (AYLS) is a part of a multicentre follow-up study conducted in Uusimaa, Finland, and Bavaria, Germany, called the Bavarian-Finnish Longitudinal Study (Heinonen et al. 2008; Salonen et al. 2015). Out of the 15 311 babies delivered in the seven maternity hospitals of Uusimaa in 1985-86, 2193 served as sample for this study: all 1535 babies admitted to neonatal wards or the Children's Hospital NICU within 10 days of birth, and 658 non-hospitalised, prospectively recruited controls born after every second hospitalised baby in one of the three largest local maternity hospitals. A total of 1913 subjects (87.2%) were traceable as adults and they received invitation to a follow-up study performed 2009–2012: 1136 subjects (59.4%, 754 hospitalised and 382 controls) participated at the mean age of 25.2 years. **Study III**

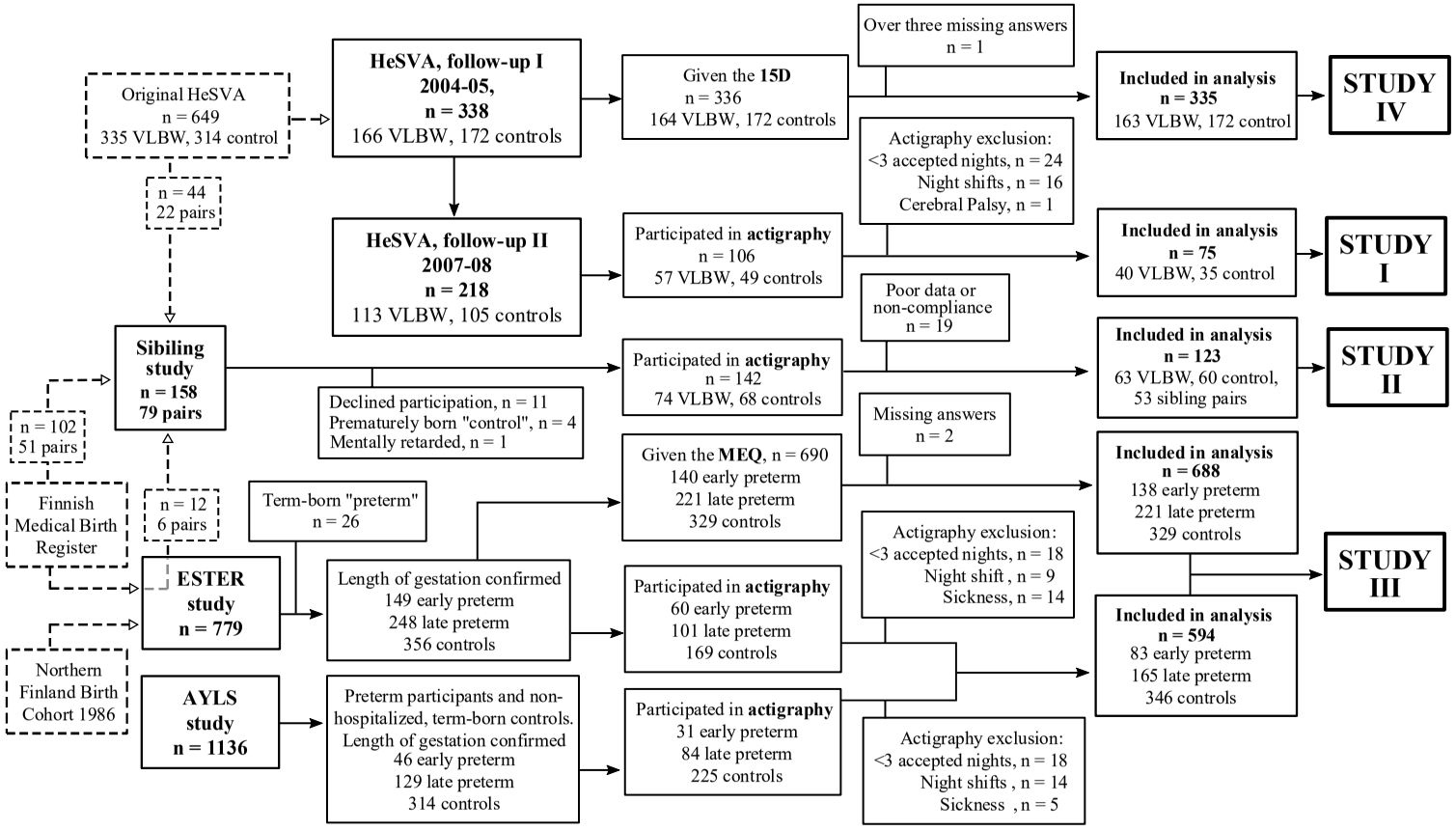
describes the quantitative chronotype and sleep of 594 participants (83 early preterm, 165 late preterm, 346 controls) from ESTER and AYLS who provided valid actigraphy data.

Figure 13. Subjects and methods for Studies I-IV.



AYLS, Arvo Ylppö Longitudinal Study; ESTER, ESTER Preterm Birth Study; HeSVA, Helsinki Study of VLBW Adults; MEQ, Morningness-Eveningness Questionnaire.

Figure 14. In-depth flowchart for source cohorts, subject exclusion, and methods used in Studies I-IV.



AYLS, Arvo Ylppö Longitudinal Study; ESTER, ESTER Preterm Birth Study; HeSVA, Helsinki Study of VLBW Adults; MEQ, Morningness-Eveningness Questionnaire; VLBW, Very Low Birth Weight.

4.2. Background variables

The perinatal data used in Study I-IV, such as birth weight, were derived from medical records as accurately as possible, with ultrasonographic determination of gestational age preferred over age-assessment by date of last menstruation. The population statistics of Pihkala et al. (1989) determined the age and sex-specific relative birth weight, with small for gestational age (SGA) defined as a birth weight of less than -2 SD, as opposed to appropriate for gestational age (AGA). Trained staff measured current status, e.g. height and weight, at the clinical visits and the participants themselves filled in the questionnaires, if possible.

4.3. How this thesis measured chronotype and sleep

Studies I-III utilized actigraphs to study quantitative chronotype, and additionally subjects in Study III completed the MEQ to establish qualitative chronotype. The specific actigraphs were in Study I Actiwatch AW4, in Study II Actiwatch2, and in Study III the ESTER participants used ActiGraph GT1M and the AYLS participants used Actiwatch AW7. All studies used one-minute epochs and medium sensitivity settings, and all subjects kept sleep diaries and used the event marker. All studies used similar scoring criteria, but specialist readers are referred to the original publications for details.

Study I & III. Subjects with NSI, night shifts, or less than three accepted nights were excluded in Study I and III (Figure 14). Because Study III was so well-powered, all subjects who reported being sick during the recording period were also excluded. The actigraphy-derived variables were aggregated, and means are reported. Study I & III lacked information about work schedules, so weekday/weekend served as proxy. Study III reports MEQ results both as the Morningness-Eveningness Score and the distribution of chronotype.

Study II. Due to the study design a different statistical method was employed (see 4.5). Because of this, individual nights, not subjects, were excluded if they contained night shift work, and nights were labelled for use of sleep medication or alcohol, taking naps, awakenings due to children, and ailments worse than the common cold. Information about work schedules were quite detailed, so weekday/weekend proxy was only required for 15% of nights. MSFsc requires calculations with means, so for that outcome nights with preceding naps, or alcohol and sleep medication use were excluded, resulting in a smaller sample size.

Harmonization. Study I concluded its data collection in 2008 and Study II in 2018, a difference of a decade. During this time the field of chronobiology and its *lege artis* methodologies evolved, so the original publications of Studies I-III do not consistently report the same outcomes, nor employ the same adjustments. This thesis will therefore attempt to harmonize the results and uniformly report the same outcomes. MSFsc will serve to describe chronotype, actual sleep duration will describe time spent asleep, and wake after sleep onset and sleep efficiency will describe sleep quality. Regression analyses will display the results from the chronobiologically most essential adjustments: sex and age, and in Study III source cohort. This thesis also investigated whether the season of birth or actigraphy period influenced preterm chronotype in a four-class photoperiod variable (spring [Feb-April], summer [May-July], autumn [Aug-Oct], and winter [Nov-Jan]), reported in 5.5. Specialist readers are referred to the original papers for excluded outcomes.

4.4. How this thesis measured HRQoL

Study IV utilized the 15D questionnaire to investigate HRQoL. It is a generic, comprehensive, and self-administered instrument based on the multi-attribute utility theory and it has proved to be reliable, sensitive, and well-validated against comparable instruments (Sintonen 1994; Sintonen 1995; Sintonen 2001, www.15d-instrument.net). Respondents estimate their performance in 15 health domains: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion (bladder and bowel function), ability to perform usual activities, mental functions, discomfort & symptoms (pain, ache, etc.), depression, distress (anxiousness etc.), feeling of vitality, and sexual activity. Each domain has one question and the respondent estimates their functioning on an ordinal 1-5 level, and an algorithm transforms the 1-5 levels into a 0-1 scale. The fifteen 0-1 values can be aggregated into a single 0-1 index (the 15D SCORE), 1 being a problem-free score, but they can also be portrayed as a profile. An algorithm can predict up to three missing answers per respondent. The minimum important difference in the 15D SCORE seems to be ±0.015, provided the finding is statistically significant, whereas ±0.035 indicates a large difference (Alanne et al. 2015). This thesis refrained from excluding subjects with NSI from the analyses but did separately compare NSI subjects to controls.

4.5. Statistical methods

Background variables. Studies I, III, and IV are case-control birth cohort studies with independent groups, and therefore employed independent samples t-test or χ^2 to determine statistically significant differences in background variables between groups. Due to the paired sibling setting in Study II, either paired t-test or McNemar's test determined statistical significance. In this thesis background characteristics were reported descriptively, however.

Study I & III. After appropriate exclusions of participants or nights (see 4.3), the actigraphy-derived sleep variables were aggregated, and means were reported. In the original papers, statistical significance was probed with independent samples t-test or Mann-Whitney U, depending on residual distribution. Linear regression models provided adjusted estimates of differences with subtly different models in the two original papers. For Study I & III this thesis first compared MSFsc between groups with independent samples t-test, and then linear regression models provided sex and age-adjusted estimates for the actigraphy variables. For the MEQ results, statistical significance was tested with χ^2 for chronotype distribution, independent samples t-test for morningness-eveningness score, and linear regression models provided sex and age-adjusted estimates of the score.

Study II. After exclusion of nights containing shift work and labelling nights for other variables, the actigraphy-derived outcomes were subjected to mixed model regression, adjusted for age (siblings were of the same sex), with repeated measurements nested within subjects, and subjects nested within families. Analysis of MSFsc requires mean values, so for this measure nights with preceding naps, alcohol use, or sleep medication were excluded before calculating the means, which were then subjected to paired t-test and mixed model regression, adjusted for age, with the measures nested within families.

Study IV. The 15D output is more skewed towards "1 – no problems" than "0 – death", and therefore Mann-Whitney U-tests probed for statistical significance in group comparisons. Means are reported instead of median, because many outcomes would have been "1", and means were thus more informative.

4.6. Power calculations

The cohorts in this thesis were formed to investigate many different outcomes, some not relevant to this thesis. Therefore, chronotype investigations did not dictate sample size calculations. Some studies performed relevant *a priori* sample size calculations, but e.g. Study III is reduced to *post hoc* calculations because it combines outcomes from two different studies. The thesis refrains from reporting "observed power", because that would simply be another way of stating the p-values (Hoenig and Heisey 2001; Lenth 2001; Lakens 2014), but it will speculate on achieved power based on sample size and estimated mean effect size from previous studies. Unless noted otherwise, α-level is 0.05, 1-β is 0.8, reported effect sizes are Cohen's d, and calculations are based on two-tailed t-tests. The software G*Power supplied all power calculations (Faul et al. 2007).

4.6.1. Chronotype

Five case-control studies had compared chronotype between preterm and term-born subjects before the first publication in this thesis. Although the studies measured the same phenomenon, they used different methods and reported different outcomes, from participants of different ages. Despite these differences, the calculated mean effect size proved useful as a rough guide for power calculations. The mean Cohen's d of the eight most relevant outcomes was ~0.41 (Table 4). Expressed in common language effect size (McGraw and Wong 1992; Ruscio 2008; Magnusson 2014), if a person is randomly picked from both the control group and

Table 4. Effect size estimation based on previous studies.

Author, year	Grade of prematurity	n, preterm/control	Method	Measure	Effect size
Hibbs et al. 2014	<37 weeks	217/284	Actigraphy	Sleep midpoint on weekends	5:17 (1:26) vs 5:41 (1:34) = **0.27**
		146/190	Self-report	Sleep midpoint on weekends	5:06 (1:17) vs 5:43 (1:35) = **0.42**
Strang-Karlsson et al. 2010	VLBW, <1500g	91/93	MEQ	Morningness-Eveningness Score	45.7 (9.6) vs 42.9 (9.0) = **0.30**
Asaka & Takada. 2010	VLBW, <1500g	14/14	Actigraphy	Sleep offset time	6:55 (0:50) vs 7:37 (1:13) = **0.67**
Strang-Karlsson et al. 2008	VLBW, <1500g	89/78	Actigraphy	Sleep onset time	23:59 (1:19) vs 0:35 (1:52) = **0.37**
		164	BNSQ	Sleep offset time, free day	9:54 (1:24) vs 10:18 (1:18) = **0.3**
Natale et al. 2005	<37 weeks	55/210	junior MEQ	Morningness-Eveningness Score	57.34 (6.44) vs 53.62 (7.47) = **0.53**
		40/318	junior CS	CS mean score	29.27 (4.94) vs 27.43 (4.84) = **0.38**
					Mean effect size = **0.41** (SD 0.14)

BNSQ, Basic Nordic Sleep Questionnaire; CS, Composite Scale; MEQ, Morningness-Eveningness Questionnaire; SD, standard deviation; VLBW, very low birth weight

the preterm group, in 61 times out of 100 the person born preterm will display an earlier chronotype.

Study I. *Post hoc.* The second follow-up study of HeSVA provided the actigraphy data for Study I. Fifty-seven VLBW subjects and 49 controls provided actigraphy data, and after relevant exclusions the participants numbered 75 (40 VLBW, 35 controls). With these figures, an effect size of 0.66 was the detection threshold. With the possible mean effect size of 0.41, the study achieved a power of 0.42. Weekend data were available for only 47 subjects (21 VLBW, 26 controls) so arguably the power could have been as low as 0.28.

Study II. *A priori & post hoc*. The sibling study attempted to recruit 80 sibling pairs and managed to recruit 79. Each subject had a matched pair, so the *a priori* numbers allowed detection of an effect size of 0.32. After dropouts and exclusions, 53 pairs provided data. With the possible mean effect size of 0.41, the study achieved a power of 0.83. MSFsc was available for 41 complete pairs, for a power of 0.73.

Study III. *Post hoc.* This was the largest study because it combined outcomes from two separate birth cohorts. Unlike Study I and II the subjects were from the whole gestation range. The previous studies that provided the mean effect size estimate mostly had VLBW subjects, or quite small subjects under the heading "preterm" in the case of Hibbs et al. (2014), so arguably the mean effect size from previous studies need not apply. For actigraphy outcomes the preterm subjects numbered 248 and controls 346. With these numbers, an effect size of 0.23 was the detection threshold. Comparing early preterm (n = 83) and late preterm (n = 163) subjects to controls (n = 341) produced effect size thresholds of 0.34 and 0.27, respectively. For MEQ results preterm subjects numbered 359 and controls 329. With these figures, an effect size of 0.21 was the detection threshold between the two groups. Comparing early preterm (n = 138) and late preterm (n = 221) subjects to controls (n = 329) produced effect size thresholds of 0.28 and 0.24. With the possible mean effect size of 0.41 even the least powered comparison, namely the weekend actigraphy data of early preterm vs control subjects (n = 76 and 306), achieved a power of 0.89. The relevance of the possible mean effect size is clearly debatable, however, due to different degree of prematurity.

4.6.2. Health-related quality of life

Alanne et al. (2015) proposed that the clinically relevant minimum important difference in the aggregate 15D SCORE is ±0.015, whereas ±0.035 constitutes a large difference. In the Health2011 study the mean 15D SCORE for 20-to-30-year-old Finns was 0.9602 (SD 0.0657, Koskinen et al. 2012; personal correspondence with Prof. Harri Sintonen). Given these numbers, a large and small difference between groups equal effect sizes of 0.53 and 0.23.

Study IV. *A priori & post hoc.* The first HeSVA follow-up, which supplied data for Study IV, attempted to recruit 140 participants to both the control and VLBW group, which would have allowed detection of effect sizes of 0.4 with a 1-β of 0.9. This choice was sound because differences of ~0.5 SD in outcomes of adult VLBW-control comparisons are not uncommon (Hovi et al. 2007; Pyhälä et al. 2011). The study managed to recruit 166 VLBW adults and 172 controls, of whom 163 and 172 completed the 15D. Given 1-β of 0.8, this provided an effect size threshold of 0.31. With the effect sizes for a large (0.53) and small (0.23) clinically relevant difference the study achieved a power of 0.998 and 0.55, respectively.

4.7. Ethical considerations

In all studies the participants provided informed and signed consent. All studies were conducted according to the Declaration of Helsinki and were approved by local ethics committees. The studies utilized anonymous IDs, and the employed methods were inherently non-invasive, consisting of questionnaire results and actigraphy recording, which is akin to wearing a bulky wristwatch.

5. RESULTS

This chapter aims to display only the most central and harmonized findings of the thesis studies. Some of the results have been specifically produced for this thesis and have not been published elsewhere, whereas some outcomes from the original papers have been omitted. In Studies I-III sleep debt-corrected sleep midpoint MSFsc serves as the central measure of chronotype, actual sleep time indicates sleep duration, and wake after sleep onset and sleep efficiency demonstrate sleep quality.

5.1. Study participants

Table 5 displays the background characteristics of all subjects in the four studies, but they are also displayed separately in the relevant study results. The least recent study is Study IV, which measured HRQoL of VLBW subjects from the HeSVA cohort at a mean age of 22.5 years: the youngest participants in this thesis. In the second follow-up study of the cohort, Study I, the mean age was 25. Study III was composed of two different cohorts, ESTER and AYLS, with subjects born in 1985-89 and 1985-86, respectively. AYLS provided proportionally more controls than ESTER, which is why their mean age was a little higher (24.5 years) than the preterm subjects' (24.0 years). The most recent Study II contained the oldest participants with a mean age of almost 30 years. Age-wise the thesis subjects therefore represent a spectrum of young adults.

In Studies II-IV the sex distribution was quite equal, ranging from 40 to 51% males, but Study I had clearly more female participants, with only 20% and 38% males in the two groups. The mean gestational age for the controls in all studies was 40 weeks, but the gestational age in the preterm groups differed by design between the VLBW groups (29 weeks) and the early and late preterm groups (32 and 36 weeks). The mean birth weight in the control group was around 3.6 kg in Studies I, III, and IV, but the controls were slightly smaller in the sibling study, at 3.4 kg. The mean birth weight for the VLBW participants was around 1.1 kg, whereas the early and late preterm subjects were naturally heavier at 1.7 and 2.7 kg. The relative birth weight of the VLBW subjects was around -1.4 SD, and the early and late preterm group had scores of -0.9 SD and -0.5 SD. The relative birth weight for the controls was expectedly centred around 0 SD except for the sibling controls, who were again slightly smaller at -0.3 SD. By design Study I and IV

Table 5. Background characteristics of thesis subjects.

	Study I, 2007-08		Study II, 2014-17		Study III, 2009-12 (actigraphy)			Study IV, 2004-05	
	Control, n = 35	VLBW, n = 40	Control, n = 60	VLBW, n = 63	Control, n = 346	Late preterm, n = 165	Early preterm, n = 83	Control, n = 172	VLBW, n = 164
Age in years, mean (SD)	24.9 (2.2)	25.0 (2.1)	29.7 (5.2)	29.9 (2.8)	24.5 (1.2)	24.0 (1.5)	24.0 (4.4)	22.5 (2.2)	22.4 (2.1)
Male, n (%)	7 (20.0%)	15 (37.5%)	29 (48.3%)	32 (50.8%)	150 (43.4%)	84 (50.9%)	38 (45.8%)	69 (40.1%)	70 (42.7%)
Gestational age in weeks, mean (SD)	40.0 (1.2)	29.2 (2.5)	39.7 (1.3)	29.4 (2.4)	40.1 (1.2)	35.8 (0.8)	31.7 (2.2)	40.1 (1.1)	29.2 (2.2)
Birth weight in grams, mean (SD)	3640 (514)	1096 (224)	3391 (452)	1135 (217)	3590 (489)	2712 (548)	1729 (472)	3593 (471)	1122 (221)
Relative birth weight in SD units, mean (SD)	0.2 (1.1)	-1.4 (1.6)	-0.3 (1.0)	-1.4 (1.6)	0.0 (1.0)	-0.5 (1.4)	-0.9 (1.3)	0.0 (1.0)	-1.3 (1.5)
Small for gestational age, n (%)	0 (0%)	15 (37.5%)	2 (3.3%)	23 (36.5%)	4 (1.2%)	20 (12.1%)	14 (16.9%)	0 (0%)	54 (32.9%)
Singleton pregnancy, n (%)	35 (100%)	35 (87.5%)	59 (98.3%)	56 (88.9%)	342 (98.8%)	142 (86.1%)	65 (78.3%)	172 (100%)	137 (83.5%)
Firstborn, n (%)*	15 (42.9%)	16 (41.0%)	20 (33.3%)	22 (34.9%)	139 (40.2%)	76 (46.1%)	40 (48.2%)	85 (49.7%)	80 (49.1%)
Maternal smoking during pregnancy, n (%)**	6 (17.1%)	7 (18.9%)	9 (17.0%)	9 (14.8%)	52 (15.2%)	29 (17.9%)	18 (22.2%)	28 (16.7%)	31 (20.1%)

*Data missing from Study IV: n = 2. **Data missing from: Study I, n = 3; Study II, n = 9; Study III, n = 8; Study IV, n = 14.
SD, standard deviation; VLBW, very low birth weight <1500 grams.

contained no controls born SGA, whereas controls in the sibling Study II and Study III had a small proportion of SGA subjects (3% and 1%). In the VLBW groups 33-38% of subjects were born SGA, compared to 17% and 12% in the early and late preterm groups. Again, by design Study I and IV contained no controls born from multiple pregnancies, whereas a diminutive proportion (<2%) were so in Studies II and III. Being first-born was more common among preterm subjects than controls in Study III. Clearly higher prevalence of maternal smoking in the preterm groups was evident in Study III (early preterm 22% vs control 15%). No subjects in Study I or III reported suffering from retinopathy of prematurity, and the data is not yet processed in Study II.

Summary. By design some variability in subject characteristics existed, especially between VLBW and early/late preterm groups. The perinatal statistics of VLBW subjects were remarkably similar across the studies, and the control groups were also quite similar, except for the sibling study controls who were somewhat smaller, possibly due to familial factors. Overall, the thesis subjects constitute a well-defined sample of young adults born preterm.

5.2. Study I

In Study I, 40 VLBW young adults and 35 term-born controls in the HeSVA cohort wore an actigraph for a mean period of 4.4 nights. Weekend measures were available for 26 controls and 21 VLBW subjects. The mean age for these young adults was 25.0 years (SD 2.2), men were underrepresented in the groups (20 and 37.5%), and by design the control group contained no subjects born SGA or from a multiple pregnancy (Table 6).

The VLBW group displayed a significantly earlier chronotype: using independent samples t-test the MSFsc was 53 min (95% CI 5 to 101 min, p = 0.032) earlier in the VLBW group (Figure 15). Adjusting for sex and age increased the difference, with the VLBW group displaying 65 min (95% CI 14 to 116 min, p = 0.013) earlier MSFsc (Table 7). The groups did not differ in sleep duration or quality.

Table 6. Study I. Subject background characteristics (n = 75).

	Control, n = 35	VLBW, n = 40
Age in years, mean (SD)	24.9 (2.2)	25.0 (2.1)
Male, n (%)	7 (20.0%)	15 (37.5%)
Gestational age in weeks, mean (SD)	40.0 (1.2)	29.2 (2.5)
Birth weight in grams, mean (SD)	3640 (514)	1096 (224)
Relative birth weight in SD units, mean (SD)	0.2 (1.1)	-1.4 (1.6)
Small for gestational age, n (%)	0 (0%)	15 (37.5%)
Singleton pregnancy, n (%)	35 (100%)	35 (87.5%)
Firstborn, n (%)	15 (42.9%)	16 (41.0%)
Maternal smoking during pregnancy, n (%)*	6 (17.1%)	7 (18.9%)

*Data missing, n = 3.
SD, standard deviation; VLBW, very low birth weight <1500 grams.

Figure 15. Study I. Unadjusted means and 95% confidence intervals of MSFsc of controls and VLBW subjects. The 21 VLBW subjects displayed 53 min (95% CI 5 to 101 min) earlier sleep midpoint than the 26 term-born controls (independent samples t-test, p = 0.032).

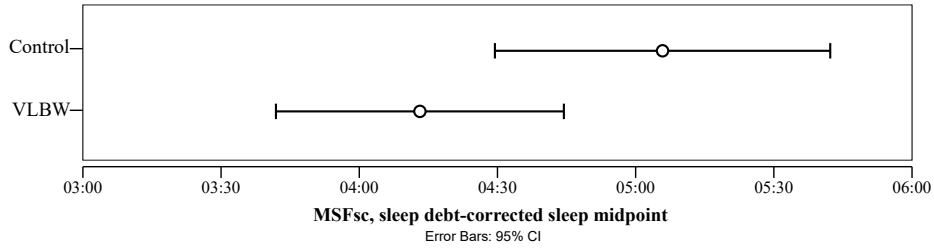


Table 7. Study I. The effect of VLBW birth on central actigraphy outcomes, adjusted for sex and age.

			Weekday Weekend	Control, n = 35 n = 26	VLBW, n = 40 n = 21
				Mean (SD)	B (95% CI)
MSFsc	Weekend	h:min:s		5:05:50 am (1:30:07)	**-1:05:23 (-1:56:25 to -0:14:21)***
Actual sleep time	Weekday	h:min:s		6:46:03 (0:45:47)	-0:05:22 (-0:29:32 to 0:18:48)
	Weekend	h:min:s		7:43:16 (1:16:23)	0:09:49 (-0:40:48 to 1:00:27)
Wake after sleep onset	Weekday	h:min:s		0:56:06 (0:27:57)	-0:05:13 (-0:17:43 to 0:07:17)
	Weekend	h:min:s		1:05:28 (0:35:29)	-0:09:51 (-0:29:31 to 0:09:50)
Sleep efficiency (%)	Weekday	%		87.8 (5.6)	0.63 (3.3 to -2.0)
	Weekend	%		87.9 (6.2)	1.18 (4.76 to -2.39)

The difference was calculated with linear regression, adjusted for sex and age.

*p < 0.05. B, regression coefficient; CI, confidence interval; MSFsc, sleep debt-corrected sleep midpoint on free days; SD, standard deviation; VLBW, very low birth weight <1500 grams.

5.3. Study II

In Study II, 63 VLBW and 60 term-born siblings (53 complete pairs) in the sibling study wore an actigraph for a mean period of 13.3 nights. Free day measures were available for 59 VLBW and 60 term-born siblings (51 complete pairs). As detailed in 4.3, calculation of MSFsc caused attrition due to exclusion of nights, leaving 52 VLBW and 53 control subjects (41 complete pairs) for this analysis. The mean age for the 123 adults was almost thirty (29.8, SD 4.1), with quite equal representation of the sexes (48.3 and 50.8% men, Table 8).

The VLBW group displayed a significantly earlier chronotype: using paired samples t-test the MSFsc was 41 minutes (95% CI 5 to 78 min, p = 0.029) earlier in the VLBW group (Figure 16). Adjustment for sex and age increased the difference, with the VLBW group displaying 46 minutes (95% CI 16 to 77 min, p = 0.004) earlier MSFsc (Table 9). The groups did not differ regarding sleep duration, but the VLBW group displayed slightly more wake after sleep onset on workdays (6 minutes, 95% CI 1 to 12 min, p = 0.023).

Table 8. Study II. Subject background characteristics (n = 123).

	Control, n = 60	VLBW, n = 63
Age in years, mean (SD)	29.7 (5.2)	29.9 (2.8)
Male, n (%)	29 (48.3%)	32 (50.8%)
Gestational age in weeks, mean (SD)	39.7 (1.3)	29.4 (2.4)
Birth weight in grams, mean (SD)	3391 (452)	1135 (217)
Relative birth weight in SD units, mean (SD)	-0.3 (1.0)	-1.4 (1.6)
Small for gestational age, n (%)	2 (3.3%)	23 (36.5%)
Singleton pregnancy, n (%)	59 (98.3%)	56 (88.9%)
Firstborn, n (%)	20 (33.3%)	22 (34.9%)
Maternal smoking during pregnancy, n (%)*	9 (17.0%)	9 (14.8%)

*Data missing, n = 9.
SD, standard deviation; VLBW, very low birth weight <1500 grams.

Figure 16. Study II. Unadjusted means and 95% confidence intervals of MSFsc of sibling controls and VLBW subjects. The comparison between 41 VLBW-control pairs showed that the VLBW group had 41 minutes (95% CI 5 to 78 min) earlier sleep midpoint (paired samples t-test, p = 0.029).

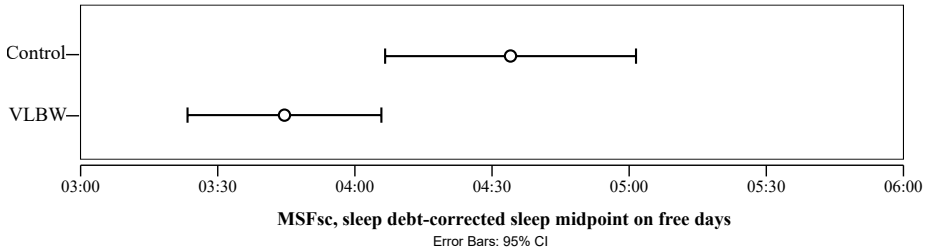


Table 9. Study II. The effect of VLBW birth on central actigraphy outcomes, adjusted for sex and age.

			Free day Workday	Control, n = 60 n = 56	VLBW, n = 59 (51 complete pairs) n = 61 (47 complete pairs)
				Mean (SD)	B (95% CI)
MSFsc	Free day†	h:min:s		4:34:02 am (1:38:32)	**-0:46:29 (-1:17:12 to -0:15:46)****
Actual sleep time	Workday	h:min:s		6:35:33 (1:20:16)	0:11:45 (-0:05:15 to 0:28:45)
	Free day	h:min:s		7:16:05 (1:20:57)	-0:06:10 (-0:23:54 to 0:11:34)
Wake after sleep onset	Workday	h:min:s		0:43:41 (0:21:31)	**0:06:24 (0:00:55 to 0:11:53)***
	Free day	h:min:s		0:59:49 (0:24:20)	0:04:57 (-0:01:43 to 0:11:36)
Sleep efficiency (%)	Workday	%		90.2 (3.8)	0.93 (2.20 to -0.34)
	Free day	%		89.6 (4.3)	1.07 (2.16 to -0.02)

The difference was calculated with mixed model regression, adjusted for sex and age.

*p < 0.05, **p < 0.01, † = 53 controls, 52 VLBW (41 complete pairs).

B, regression coefficient; CI, confidence interval; MSFsc, sleep debt-corrected sleep midpoint on free days; SD, standard deviation; VLBW, very low birth weight <1500 grams.

5.4. Study III

Actigraphy. In Study III, 346 controls, 165 late preterm, and 83 early preterm subjects from the combined ESTER and AYLS cohorts wore an actigraph for a mean period of 6.8 nights (ESTER 6.5, AYLS 7.0). Weekend measures were available for 306 controls, 142 late preterm, and 76 early preterm subjects. The mean age for these young adults was 24.3 years (SD 2.0), with somewhat equal representation of sexes (43.4-50.9%, Table 10).

As is evident from Figure 17 and Table 11, no significant differences emerged between the preterm groups and the control group in measures of chronotype, sleep duration, or sleep quality. Additional sensitivity analyses by cohort did not uncover any differences either.

Table 10. Study III. Actigraphy subjects background characteristics (n = 594).

	Control, n = 346	Late preterm, n = 165	Early preterm, n = 83
Age in years, mean (SD)	24.5 (1.2)	24.0 (1.5)	24.0 (4.4)
Male, n (%)	150 (43.4%)	84 (50.9%)	38 (45.8%)
Gestational age in weeks, mean (SD)	40.1 (1.2)	35.8 (0.8)	31.7 (2.2)
Birth weight in grams, mean (SD)	3590 (489)	2712 (548)	1729 (472)
Relative birth weight in SD units, mean (SD)	0.0 (1.0)	-0.5 (1.4)	-0.9 (1.3)
Small for gestational age, n (%)	4 (1.2%)	20 (12.1%)	14 (16.9%)
Singleton pregnancy, n (%)	342 (98.8%)	142 (86.1%)	65 (78.3%)
Firstborn, n (%)	139 (40.2%)	76 (46.1%)	40 (48.2%)
Maternal smoking during pregnancy, n (%)*	52 (15.2%)	29 (17.9%)	18 (22.2%)

*Data missing, n = 8.
SD, standard deviation.
Late preterm 34 to <37 weeks, early preterm <34 weeks.

Figure 17. Study III. Unadjusted means and 95% confidence intervals of MSFsc of the control group (n = 306), the late preterm group (34 to <37 weeks, n = 142), and the early preterm group (<34 weeks, n = 76). No significant differences emerged between the groups.

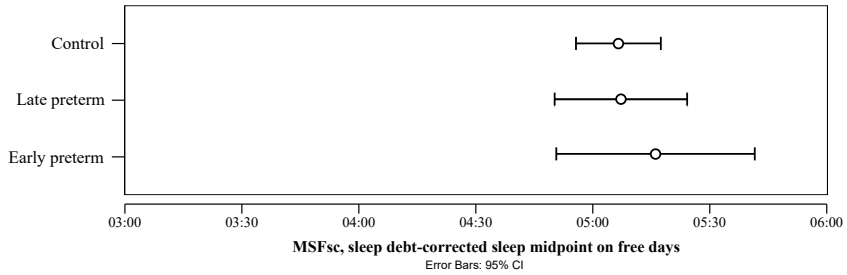


Table 11. Study III. The effect of late and early preterm birth on central actigraphy outcomes, adjusted for sex and age.

		Weekday Weekend	Control, n = 346 n = 306	Late preterm, n = 165 n = 142	Early preterm, n = 83 n = 76
			Mean (SD)	B (95% CI)	B (95% CI)
MSFsc	Weekend	h:min:s	5:06:27 am (1:36:36)	-0:06:25 (-0:26:21 to 0:13:31)	0:03:36 (-0:21:34 to 0:28:45)
Actual sleep time	Weekday	h:min:s	6:58:32 (0:57:38)	-0:02:35 (-0:12:59 to 0:07:50)	0:06:54 (-0:06:34 to 0:20:22)
	Weekend	h:min:s	7:16:02 (1:12:18)	0:13:48 (-0:01:19 to 0:28:54)	0:08:33 (-0:10:31 to 0:27:38)
Wake after sleep onset	Weekday	h:min:s	0:59:15 (0:28:45)	-0:01:36 (-0:06:39 to 0:03:27)	0:00:38 (-0:05:54 to 0:07:10)
	Weekend	h:min:s	1:02:42 (0:36:20)	0:02:02 (-0:05:03 to 0:09:7)	0:03:32 (-0:05:24 to 0:12:28)
Sleep efficiency (%)	Weekday	%	85.7 (5.5)	0.05 (1.0 to -0.9)	0.26 (1.5 to -0.97)
	Weekend	%	85.7 (6.7)	-0.43 (0.9 to -1.7)	-0.70 (0.9 to -2.3)

The difference was calculated with linear regression, adjusted for sex, age, and source cohort.
B, regression coefficient; CI, confidence interval; MSFsc, sleep debt-corrected sleep midpoint on free days; SD, standard deviation.
Late preterm 34 to <37 weeks, early preterm <34 weeks.

Morningness-Eveningness Questionnaire. In Study III, 329 controls, 221 late preterm, and 138 early preterm subjects from the ESTER cohort completed the Morningness-Eveningness Questionnaire. The mean age for these young adults was 23.3 years (SD 1.2), with somewhat equal representation of sexes (44.9-50.2%, Table 12).

As is evident from Figure 18 and Table 13, no significant differences emerged between the preterm groups and the control group regarding the Morningess-Eveningness Score. The MEQ classified 12.4% of the subjects as morning types, 65.4% as intermediate, and 22.2% as evening types; further subclassification revealed that 0.7% were definite morning types and 3.5% were definite evening types. Neither the three-group nor the five-group distribution differed significantly between the control, late preterm, and early preterm groups when measured with χ^2-tests.

Table 12. Study III. MEQ subjects background characteristics (n = 688).

	Control, n = 329	Late preterm, n = 221	Early preterm, n = 138
Age in years, mean (SD)	23.5 (1.1)	23.1 (1.3)	23.0 (1.4)
Male, n (%)	155 (47.1%)	111 (50.2%)	62 (44.9%)
Gestational age in weeks, mean (SD)	40.0 (1.2)	35.8 (0.8)	31.7 (2.0)
Birth weight in grams, mean (SD)	3570 (485)	2671 (524)	1752 (482)
Relative birth weight in SD units, mean (SD)	0.0 (1.0)	-0.6 (1.3)	-1.0 (1.4)
Small for gestational age, n (%)	6 (1.8%)	27 (12.2%)	25 (18.1%)
Singleton pregnancy, n (%)	325 (98.8%)	190 (86.0%)	107 (77.5%)
Firstborn, n (%)	103 (31.3%)	93 (42.1%)	53 (38.4%)
Maternal smoking during pregnancy, n (%)*	51 (15.7%)	41 (19.0%)	21 (16.0%)

*Data missing, n = 16.
MEQ, Morningness-Eveningness Questionnaire; SD, standard deviation.
Late preterm 34 to <37 weeks, early preterm <34 weeks.

Figure 18. Study III. Unadjusted means and 95% confidence intervals of Morningness-Eveningness Score of the control group (n = 339), the late preterm group (34 to <37 weeks, n = 221), and the early preterm group (<34 weeks, n = 138). No significant differences emerged between the groups.

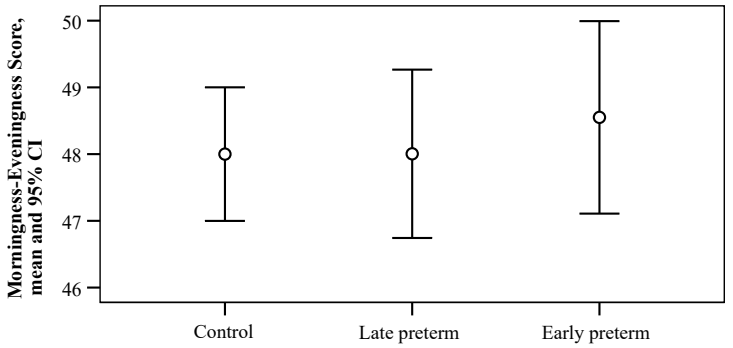


Table 13. Study III. The effect of late and early preterm birth on Morningess-Eveningness Score (n = 688).

	Control, n = 329	Late preterm, n = 221	Early preterm, n = 138
	Mean (SD)	B (95% CI)	B (95% CI)
Morningness-Eveningness Score	48.0 (9.2)	0.1 (-1.5 to 1.7)	0.6 (-1.3 to 2.4)

The difference was calculated with linear regression, adjusted for sex and age.
B, regression coefficient; CI, confidence interval; SD, standard deviation.
Late preterm 34 to <37 weeks, early preterm <34 weeks.

5.5. Summary of studies I-III

In both Study I and II, which consisted of controls and preterm subjects born VLBW, the preterm group displayed a robustly earlier chronotype than the control group, by a measure of 46 to 65 minutes in the regression models. No differences in sleep duration were apparent in either study. Study II found that wake after sleep onset was 6 minutes longer in the VLBW group, but a poorer sleep quality was not supported by the sleep efficiency, or the sleep quality results in Study I. Study III, which consisted of controls, late preterm subjects, and early preterm subjects, did not reveal any significant difference between the groups in quantitative or qualitative chronotype, sleep duration, or sleep quality. MSFsc and gestational age did not reveal any relationship (Figure 19). Addition of photoperiod (birth or actigraphy period) in the regression models of the three studies had only a negligible effect on preterm chronotype, shifting MSFsc by at most three minutes (not shown). Figure 20 and Table 14 display the results side-by-side to assist comparison of study outcomes, but with the caveat that the displayed outcomes were not subjected to identical exclusions or statistical methods.

Figure 19. Study III. Scatterplot of MSFsc by gestational age in weeks (n = 524). No association between the two variables was apparent.

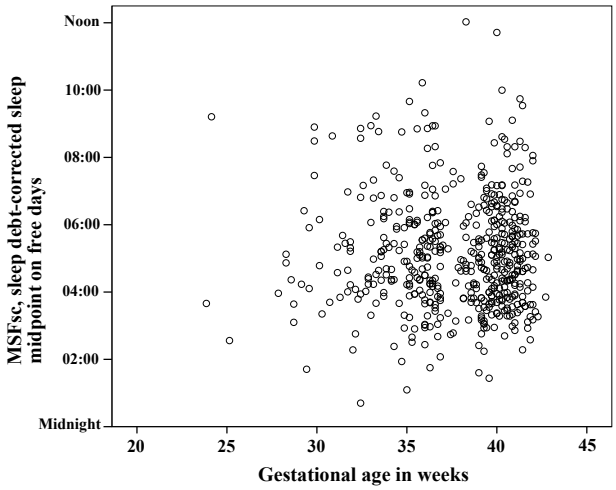


Figure 20. Merged figure of unadjusted means and 95% confidence intervals of sleep debt-corrected sleep midpoint on free days (MSFsc) from Studies I-III. The studies are ordered according to age to show the natural age-related advancement of chronotype. Late and early preterm groups (34 to <37 weeks and <34 weeks, Study III) did not differ from controls, but very low birth weight subjects (VLBW, Study I & II) displayed a significantly earlier chronotype than controls.

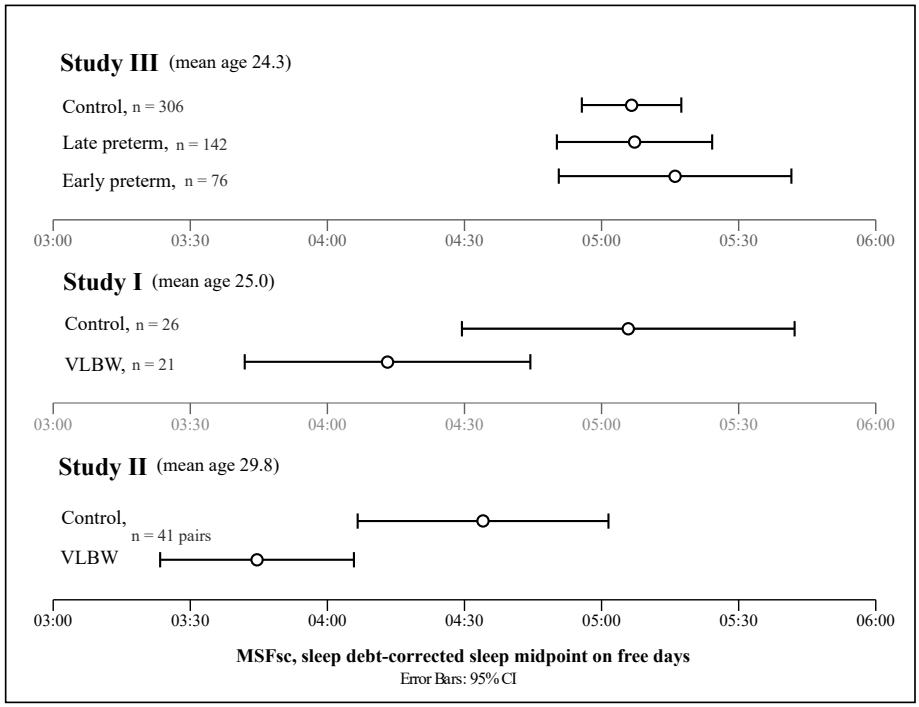


Table 14. Combined actigraphy outcomes from Studies I-III, adjusted for sex and age.

		MSFsc, sleep debt-corrected sleep midpoint on free days, h:min:s	**ACTUAL SLEEP TIME** Week-/Workday, h:min:s	Weekend/Free days, h:min:s
STUDY III	Control, mean (SD)	5:06:27 am (1:36:36)	6:58:32 (0:57:38)	7:16:02 (1:12:18)
	Late preterm, B (95% CI)	-0:06:25 (-0:26:21 to 0:13:31)	-0:02:35 (-0:12:59 to 0:07:50)	0:13:48 (-0:01:19 to 0:28:54)
	Early preterm, B (95% CI)	0:03:36 (-0:21:34 to 0:28:45)	0:06:54 (-0:06:34 to 0:20:22)	0:08:33 (-0:10:31 to 0:27:38)
STUDY I	Control, mean (SD)	5:05:50 am (1:30:07)	6:46:03 (0:45:47)	7:43:16 (1:16:23)
	VLBW, B (95% CI)	**-1:05:23 (-1:56:25 to -0:14:21)***	-0:05:22 (-0:29:32 to 0:18:48)	0:09:49 (-0:40:48 to 1:00:27)
STUDY II	Control, mean (SD)	4:34:02 am (1:38:32)	6:35:33 (1:20:16)	7:16:05 (1:20:57)
	VLBW, B (95% CI)	**-0:46:29 (-1:17:12 to -0:15:46)****	0:11:45 (-0:05:15 to 0:28:45)	-0:06:10 (-0:23:54 to 0:11:34)

		WAKE AFTER SLEEP ONSET Week-/Workday, h:min:s	Weekend/Free days, h:min:s	**SLEEP EFFICIENCY** Week-/Workday, %	Weekend/Free days, %
STUDY III	Control, mean (SD)	0:59:15 (0:28:45)	1:02:42 (0:36:20)	85.7 (5.5)	85.7 (6.7)
	Late preterm, B (95% CI)	-0:01:36 (-0:06:39 to 0:03:27)	0:02:02 (-0:05:03 to 0:09:7)	0.05 (1.0 to -0.9)	-0.43 (0.9 to -1.7)
	Early preterm, B (95% CI)	0:00:38 (-0:05:54 to 0:07:10)	0:03:32 (-0:05:24 to 0:12:28)	0.26 (1.5 to -0.97)	-0.70 (0.9 to -2.3)
STUDY I	Control, mean (SD)	0:56:06 (0:27:57)	1:05:28 (0:35:29)	87.8 (5.6)	87.9 (4.7)
	VLBW, B (95% CI)	-0:05:13 (-0:17:43 to 0:07:17)	-0:09:51 (-0:29:31 to 0:09:50)	0.63 (3.3 to -2.0)	1.18 (4.76 to -2.39)
STUDY II	Control, mean (SD)	0:43:41 (0:21:31)	0:59:49 (0:24:20)	90.2 (3.8)	89.6 (4.3)
	VLBW, B (95% CI)	**0:06:24 (0:00:55 to 0:11:53)***	0:04:57 (-0:01:43 to 0:11:36)	0.93 (2.20 to -0.34)	1.07 (2.16 to -0.02)

The difference was calculated with linear regression in Study I & III, and mixed model regression in Study II, all adjusted for sex and age.
*p < 0.05, **p <0.01. B, regression coefficient; CI, confidence interval; SD, standard deviation; VLBW, very low birth weight <1500 grams.
Late preterm 34 to <37 weeks, early preterm <34 weeks.

5.6. Study IV

In this study 172 controls and 164 VLBW adults completed the 15D questionnaire. Of the preterm subjects, 110 were born AGA and 54 SGA. Twenty-one subjects reported having one or more neurosensory impairments (14 CP, 5 developmental disability, 5 visual, and 1 hearing impairment), and they were not excluded from the analyses. For one subject born AGA-VLBW the 15D SCORE could not be calculated due to more than three missing answers. The mean age for these young adults was 22.5 years (SD 2.1), men were a little underrepresented in the groups (40.1 and 42.7%), and by design the control group had no subjects born SGA or from a multiple pregnancy (Table 15).

The VLBW group did not differ from the control group in any of the 15 dimensions nor the aggregate 15D SCORE. The NSI-subjects did not score a lower aggregate 15D SCORE than controls, but did score lower on the dimensions of mobility, vision, eating, and sexual activity (not shown in figures). HRQoL analysis by relative birth weight and sex is detailed in the subsequent pages.

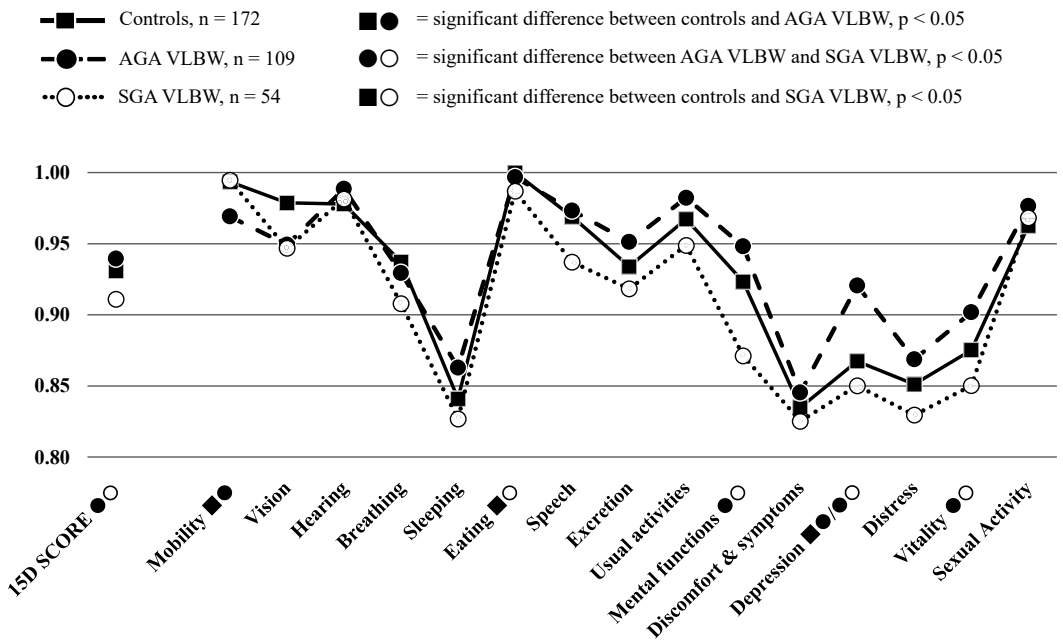
Table 15. Study IV. Subject background characteristics (n = 336).

	Control, n = 172	VLBW, n = 164
Age in years, mean (SD)	22.5 (2.2)	22.4 (2.1)
Male, n (%)	69 (40.1%)	70 (42.7%)
Gestational age in weeks, mean (SD)	40.1 (1.1)	29.2 (2.2)
Birth weight in grams, mean (SD)	3593 (471)	1122 (221)
Relative birth weight in SD units, mean (SD)	0.0 (1.0)	-1.3 (1.5)
Small for gestational age, n (%)	0 (0%)	54 (32.9%)
Singleton pregnancy, n (%)	172 (100%)	137 (83.5%)
Firstborn, n (%)*	85 (49.7%)	80 (49.1%)
Maternal smoking during pregnancy, n (%)**	28 (16.7%)	31 (20.1%)

*Data missing, n = 2. **Data missing, n = 14.
SD, standard deviation; VLBW, very low birth weight <1500 grams.

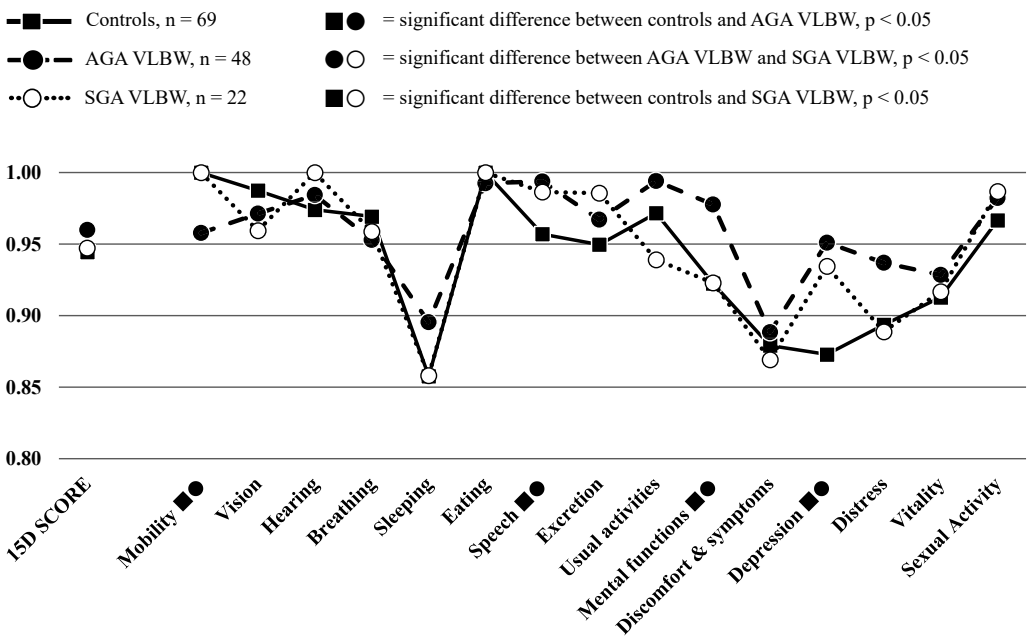
Subdivision by relative birth weight revealed that the 15D SCORE of the SGA-VLBW group was significantly lower than that of the AGA-VLBW group, and the difference exceeded the minimum important difference (0.911 versus 0.939, Δ0.028, p = 0.039, Figure 21). The AGA-VLBW group scored better than the SGA-VLBW group in the dimensions of mental functions, depression, and vitality. The AGA-VLBW group scored worse than controls in mobility, and better than controls in depression. The SGA-VLBW group scored worse than controls in eating.

Figure 21. 15D SCORE and profile of VLBW adults born small and appropriate for gestational age (SGA, AGA), and controls. VLBW adults born SGA reported a significantly worse 15D SCORE than AGA-VLBW adults. This difference exceeded the threshold for a minimum important clinical difference.



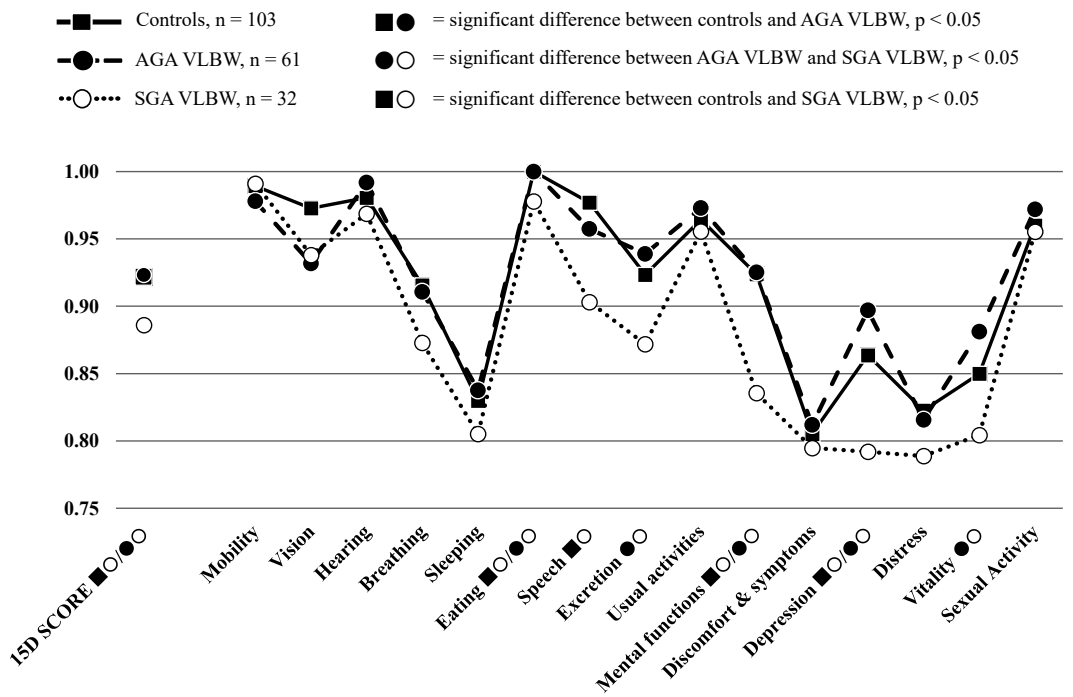
No difference emerged in the aggregate 15D SCORE between SGA-VLBW men, AGA-VLBW men, and control men. AGA-VLBW men scored lower than controls in mobility, but better in speech, mental functions, and depression.

Figure 22. 15D SCORE and profile of male VLBW adults born small and appropriate for gestational age (SGA, AGA), and controls. VLBW men in general, and AGA-born in particular, scored quite well in several subdomains.



VLBW women born SGA scored poor results in many dimensions: the 15D SCORE difference exceeded the threshold for a large clinical difference both in comparison to control women (0.886 versus 0.922, Δ0.036, p = 0.018) and AGA-VLBW women (0.886 versus 0.923, Δ0.037, p = 0.025). SGA-VLBW women scored lower than just controls in speech, lower than just AGA-VLBW women in excretion and vitality, and lower than both control and AGA-VLBW women in eating, mental functions, and depression.

Figure 23. 15D SCORE and profile of female VLBW adults born small and appropriate for gestational age (SGA, AGA), and controls. VLBW women born SGA reported worse HRQoL than AGA-VLBW women and control women in many dimensions, and in the aggregate 15D SCOREs.



6. DISCUSSION

Is a very low birth weight (<1500 grams) preterm birth associated with chronotype, sleep duration, or sleep quality at adult age?

In Studies I and II measurement of objective sleep timing with actigraphs revealed that VLBW is associated with an earlier chronotype. The findings from Study I were essentially replicated in Study II, which utilized an improved and more rigorous methodology. No difference in sleep duration emerged, but workday wake after sleep onset was higher in the VLBW group in Study II. This finding should not necessarily be interpreted as poorer sleep quality *per se*, because the sleep efficiency did not differ between the groups, and the VLBW group also displayed almost 12 min longer actual sleep on workday nights, albeit non-significantly.

These findings fall neatly in line with the few chronotype/sleep studies performed on VLBW young adults, namely Strang-Karlsson et al.'s two studies in the HeSVA cohort (2007; 2010). The first study showed that VLBW young adults (22.4 years) displayed 36 min earlier actigraphy-derived bedtime, and 24 min earlier awakening on weekends by self-report. The study did not discover any difference in sleep duration or quality. The later study utilized the MEQ and found that VLBW young adults (~25 years) reported stronger morningness tendencies, with a difference of 2.8 in the Morningness-Eveningness Score.

In younger subjects, not a single study across the age spectrum indicates a later chronotype in preterm subjects born very preterm or earlier, but most suggest an earlier chronotype (see 2.2.7, Table 1). Regarding sleep duration and sleep quality of subjects born very preterm/VLBW or earlier, no studies on adolescents exist, and comparing results from infants, toddlers, and young children to adults is quite questionable. Also, the studies comparing young preterm subjects to controls show highly contradictory results regarding sleep duration and quality, so our findings of no difference are supported by some studies and contradicted by others (2.3.4, Table 2).

Is preterm birth from the whole gestation range (<37 weeks) associated with chronotype, sleep duration, or sleep quality at adult age?

Study III measured the timing, duration, and quality of sleep with actigraphs, and subjective chronotype with the MEQ in a well-powered sample of preterm subjects from the whole preterm range. It did not discover a difference in chronotype, sleep duration, or sleep quality compared to term-born controls.

Most similar studies have focused on quite small preterm survivors, at VP/VLBW or earlier, with only few studies from the whole preterm range, namely two studies performed on adolescents (Natale et al. 2005; Hibbs et al. 2014), and one study on toddlers (Caravale et al. 2017). The two studies with adolescents seemingly contradict our findings of no difference in chronotype. The preterm 13-year-olds in Natale et al.'s questionnaire study demonstrated a stronger tendency towards morningness than term-born controls. The mean birth weight and gestational age in the study were 1738 grams and 34.8 weeks, which in terms of weight is comparable with the early preterm group in Study III (1752 g). The adolescents in Hibbs et al.'s study were ~18 years old, and they displayed earlier sleep timing both with self-report and actigraphy. Like Study III, that study did not find a difference in sleep duration, but unlike Study III, sleep quality differed and was in fact better in the preterm group, as evidenced by fewer nightly awakenings and less sleepiness in the morning. These preterm subjects in Hibbs et al. (2014) were technically from the whole range of prematurity, but many subjects were clearly on the small and early side of the spectrum, with a mean birth weight of 1514 g and gestational age of 31 weeks, compared to the early preterm group in Study III (1752 g and 32 weeks). So, the preterm subjects in these two studies on adolescents are most comparable either to the early preterm group in Study III, or an even earlier degree of prematurity in Hibbs et al., where a substantial portion of the subjects must have been born VLBW (<1500 g). In either case, both studies investigated adolescents, unlike Study III where the subjects were young adults. Therefore, the comparison to the results in Study III is not straightforward, and arguably the results need not be in conflict.

The sleep studies of preterm infants, toddlers, and young children again show such high variability that a comparison to our adult thesis subjects is questionable. In short, some studies show differences in sleep attributes, and others do not, so our findings are both supported and contradicted by these studies (2.3.4, Table 2).

Is a very low birth weight (<1500 grams) preterm birth associated with poorer health-related quality of life at adult age?

Study IV measured HRQoL of VLBW young adults and controls and found mixed results. Overall, the results did not differ between the two groups, but intriguing findings arose in the subgroup comparisons: VLBW subjects born SGA scored poorer than VLBW subjects born AGA in the aggregate 15D SCORE, with no differences to the control group. The difference exceeded the minimum important difference, and the profile revealed differences between the AGA-VLBW and SGA-VLBW group in depression, mental functions, and vitality. Overall the AGA-VLBW group scored better than expected, even better than controls in depression, but worse in mobility. Further subanalysis by sex was illuminating and revealed two trends that possibly caused the disjunctive findings: 1) AGA-VLBW men scored surprisingly well, even better than controls in speech, mental functions, and depression, but worse in mobility 2) SGA-VLBW women scored poorly in six of the fifteen dimensions (speech, eating, excretion, mental functions, depression, and vitality), causing an aggregate 15D SCORE so low as to constitute a 'large important difference' in comparison to both controls and AGA-VLBW women. This difference was unlikely caused by NSI-subjects, who reported poorer scores in mostly other dimensions (mobility, vision, eating, and sex).

Section 2.5.2. outlined results from 23 QoL studies of adults born preterm, mostly at stark degrees of prematurity. None of them used the 15D instrument, so no direct comparison is available. Unlike most recent studies (Båtsvik et al. 2015; Baumann et al. 2016; Husby et al. 2016; Saigal et al. 2016), Study IV did not discover a difference on the preterm/control level, nor between NSI-subjects and controls. Previous studies support our subgroup findings: Vederhus et al. (2015) reported no difference in overall HRQoL, but noted better self-esteem and role/social-emotional among preterm boys, and lower self-esteem among girls. Several studies have noted that preterm men score lower on physical functioning (Cooke 2004; Saigal et al. 2007; Baumgardt et al. 2012), and Lund et al. (2012) found that term-born SGA subjects had lower scores for mental health, social functioning, and emotional role.

The variable findings in this thesis give credence to a nuanced approach regarding quality of life studies, because had the analysis stopped at the VLBW/control level all subgroups details would have gone unnoticed.

Limitations and strengths

Limitations. In some ways these studies forged new ground, and hopefully their flaws can help future investigations avoid the same problems. Firstly, adequate power is important. Section 4.6. displays relevant power calculations, and they reveal that discovering a statistically significant chronotype difference in Study I was unlikely, with power possibly as low as 0.28. Secondly, quantity does not necessarily trump quality. Long registration periods are important to capture enough free day data to avoid participant exclusions in the analysis, and comprehensive sleep diaries allow accurate labelling of nights. For example, Study I and III did not specifically ask about free and workdays so weekend/weekday served as proxy, but in Study II almost 8% of workdays occurred on weekends, so this distinction is important. Thirdly, our method for dealing with complications like night shifts was exclusion of subjects or nights, which handles the problem crudely, and might produce overly polished results. Fourthly, the actigraphy studies did not gather information about exposure to zeitgebers like sunlight. Such data could have helped determine if the difference in sleep timing was due to different environmental entrainment. Fifthly, this thesis lacked some important variables, such as information about co-sleeping. Sixthly, although Study III was well-powered, it combined data from two different studies and actigraphs. Adjustment for source cohort theoretically tackled this problem, but nevertheless some bias could remain. Seventhly, actigraphs are unrivalled at determining longitudinal sleep timing, but outcomes like sleep quality are less reliable. As a final point, no previous studies have used the 15D instrument to query HRQoL, so while the instrument itself is valid, a direct comparison to previous studies was not possible.

Strengths. Study II revealed the strength of the sibling setting: it provided good power with relatively few subjects, and the limited number of subjects facilitated quite detailed phenotyping. Also, the sibling setting circumvents many family-based confounders. Methodologically Study II was the soundest with a mean registration period of almost two weeks. Actigraphy allowed analysis of objective data, unlike inherently less accurate self-reports. The populations in the thesis studies were well-defined, with reliable and accurate perinatal data, which was possible because the Finnish health care system is globally one of the foremost both in gathering data and in accommodating its use in research.

Implications of the results

Chronotype. Section 2.2.5. describes how an earlier chronotype is associated with beneficial outcomes, so the earlier chronotype in VLBW subjects is likely a protective factor, but this has not been directly demonstrated in this population. The fact that only VLBW subjects displayed an earlier chronotype, and not subjects from later degrees of prematurity, suggests that the phenomenon is related to more disruptive early exposures.

Sleep. The results regarding sleep duration and quality are altogether encouraging. Sufficiently long and restful sleep is important for health and wellbeing, and none of the preterm groups in Studies I-III displayed shorter sleep duration or convincingly poorer sleep quality. This argues against long-term detriments in these sleep-related attributes.

HRQoL. The results from Study IV did not provide a simple answer. It is encouraging that in contrast to other recent studies, overall the VLBW group did not differ from controls regarding HRQoL. The subgroup analysis revealed considerable differences between subgroups, however, particularly that VLBW women born SGA scored poorly and might constitute a group that could benefit from additional focus and aid.

Speculations

Why would a premature birth program an earlier chronotype? The question can be viewed through different developmental plasticity models, that usually belong to one of two camps: 'development constraints' models and 'predictive' models. Development constraints models like the 'thrifty phenotype hypothesis' generally describe adaptive strategies that improve immediate survival at the possible expense of later health, whereas predictive models like the 'predictive adaptive response' suggest that the early cues an organism experiences induce responses that increase fitness for a later environment (Lea et al. 2017). So, firstly, the earlier chronotype could be a primary response that increases immediate survival and might also have a later incidental advantage, with some possible trade-off. Secondly, the fetus might interpret an early stressor as a cue for a future environment in which an earlier chronotype is beneficial. It is also possible that the earlier chronotype might not be a primary response to a stressor, but a by-product of another response. Hypothetically, an earlier chronotype could provide a temporal niche, which might increase fitness. Apart from adaptive responses, stressors can also cause non-

adaptive and disruptive responses without redeeming qualities (Gluckman et al. 2005). There is no evidence that an earlier chronotype would be harmful, so it is unlikely a direct disruptive response, but it could be a by-product of a disruptive response. So, in summary, the earlier chronotype could arguably be an adaptive response (or a by-product of one) to an early stressor, or it might be a by-product of a disruptive response.

What could cause the earlier rhythm? Roenneberg et al. (2003) describe three chronobiological reasons why phase of entrainment might differ: 1) different efficiency in the reception or transduction of zeitgeber signals, 2) difference in free-running period, or 3) different coupling between the circadian clock and the measured output. If we assume that some prematurity-related exposure causes an earlier phase of entrainment, here are some ways is could do so: it could cause stronger transduction of zeitgeber effects that advance the internal clock, it could cause a shorter period, it could induce stronger advancing phase shift responses to zeitgebers, and it could cause more imminent couplings between the circadian clock and measured outputs. It is also possible that behavioural traits explain the earlier chronotype; VLBW adults are more conscientious (Pesonen et al. 2008), and report stricter upbringing (Pyhälä et al. 2011), both of which are associated to earlier chronotype (Randler et al. 2009; Tonetti et al. 2009; Duggan et al. 2014). Conscientiousness might also promote chronobiologically advancing behaviour, such as being more outdoors.

Why did HRQoL vary between subgroups? Male and female VLBW preterms scored quite differently in HRQoL in Study IV, with especially AGA-VLBW men scoring well, and SGA-VLBW women scoring poorly. One reason for this discrepancy might be survivor bias: male infants have higher rates of mortality and disability (Kent et al. 2012). So, death of the least viable male infants, lesser participation of NSI-subjects, and lesser male participation might explain why the remaining preterm men scored so well. Why AGA-VLBW men scored lower on mobility, and SGA-VLBW women scored low on speech, eating, excretion, mental functions, depression, and vitality might illustrate the concentration of problems into these dimensions, or it might reflect gendered insecurities.

Implications for future research

Future studies investigating chronotype in preterm populations would benefit the research community if they focused on investigating why the link might exist, and whether it is beneficial. Chronobiologists could investigate entraining behaviour, such as exposure to sunlight, eating rhythms, and timing of social activities, sleep labs could compare dim-light melatonin onset and investigate if the period or phase shift responses differ in preterm subjects, psychological studies could investigate the role of conscientiousness, and laboratory tests could investigate possible genetic or epigenetic differences in chronotype genes. Polysomnographic data would be useful to uncover possible differences in sleep quality. Quality of life research has been very focused on HRQoL, and "pure" QoL research would be interesting. This author would also like to see more reporting of QoL outcomes according to relative birth weight. It is becoming increasingly tenuous to assume that adults born preterm three or four decades ago represent the future of today's survivors, so comparing results to newer and younger cohorts could highlight the progress that has hopefully taken place. Nevertheless, the health of these preterm young adults will begin to deteriorate as they pass their youthful prime, possibly faster than for controls, so continued investigation of their QoL is also important. The fact that more recent studies show poorer HRQoL as the preterms grow older and the methodologies improve is of course worrying and should galvanize the research community.

7. CONCLUSIONS

1. Is a very low birth weight (<1500 grams) preterm birth associated with chronotype, sleep duration, or sleep quality at adult age?

Objective measurement of sleep with actigraphs revealed that a very low birth weight is associated with an earlier chronotype in adults born preterm, but sleep duration and quality do not differ.

2. **Is preterm birth from the whole gestation range (<37 weeks) associated with chronotype, sleep duration, or sleep quality at adult age?**

   Measurement of objective sleep timing and subjective chronotype did not reveal any differences in chronotype, nor did sleep duration or sleep quality differ in preterm young adults born at more moderate degrees of prematurity.

3. **Is a very low birth weight (<1500 grams) preterm birth associated with poorer health-related quality of life at adult age?**

   Assessment with the 15D instrument did not reveal poorer health-related quality of life in very low birth weight young adults in general, but analysis by sex and relative birth weight revealed that preterm women born small for gestational age reported markedly poorer scores.

8. ACKNOWLEDGEMENTS

As I'm vacantly staring out of my home office window, having joined together some thirty thousand words into a thesis, I arrive to the acknowledgements chapter. I don't usually dwell on the past, but I can't help but wonder how I got here. My research work has been a constant companion for a long time, and it's difficult to disentangle it from the rest of my life. I want to extend words of gratitude to everyone who has helped me on this journey, but I don't even know where to begin. Well, to quote advice from Alice in Wonderland:

> 'Begin at the beginning,' the King said, very gravely,
> 'and go on till you come to the end: then stop.'

Mom, Dad, thank you. Your upbringing has combined two aspects that don't necessarily come as a package: you have always supported me fully, without really caring about what I do, as long as I challenge myself. Dear brother and sister, thank you for also always supporting me in my strange endeavours.

From here I'll jump to a consequential meeting in the Children's Hospital in the spring of 2009. By some act of providence I had sent an e-mail to Sture Andersson, asking if I could do my obligatory medical advanced studies in his team. Below you can see my application in its entirety: it was a full three sentences long, contained at least two grammatical errors, and for frail Swedish-teachers the sentence structure could prove fatal.

> *"Hej,*
> *mitt namn är Johan Björkqvist och jag studerar i medicinska fakultetet för andra året. Jag tänkte börja med mina fördjupade studier den här sommaren och jag har förstått att ni har en svenskspråkig forskningsgrupp i neonatologi. Om så är fallet skulle jag vara intresserad av att söka till den, tror ni att detta är möjligt?*
> *h: Johan Björkqvist, L2"*

Sture, you are possibly the most disarming person I know. Although I was a nervous young medical student, you instantly made me feel welcome. I can still remember after all these years, how I didn't know if you were serious or only joking when you said to me in this very first meeting: "and after this you'll of course continue to do a dissertation for us". Well here we are.

In that same meeting was also a third person, who would have the greatest impact on my academic journey. Sonja Strang-Karlsson, I can honestly say that this book wouldn't exist without you. Without hesitation you took me under your wing and with seemingly endless patience, kindness, and insight guided me through the advanced studies, which later become my first publication with you deservedly as the senior author. A nudge on the steering wheel at an early stage can lead to unexpected destinations years later, and your massive effort during those crucial early years have led to this book you are now holding in your hands.

If Sture and Sonja sent me in the right direction, it was my three supervisors that took care of me during the long journey, at times gently directing forward, or at times grabbing me by the hand and pulling me onwards if I was being especially thick.

Eero Kajantie, you are the quintessential scientist. Your curiosity, patience, attention to detail, and breadth of knowledge are staggering, and you have the capacity to see any issue from any angle. I am grateful for the countless times you have provided council, of matters great and small, because I really have contacted you a lot during the years: a search in my "Sent"-folder revealed that I have sent you close to 400 e-mails!

Anu Pesonen, you are a dynamic force in the world of research, and a problem solver by nature. Whenever I get stuck in obstacles you instantly understand what is important and set me on the right path. You also notice details that others pass by, as seen in your photography. I respect your honesty, your deep understanding of my thesis subjects, and your open appreciation of the beautiful things in life like art, music, and literature.

Petteri Hovi, while you have an impeccable academic resumé, your most striking features are your social skills, that to a socially anxious person like me borders on insanity. Your one-on-one mini-lectures about high-level statistics leave me scratching my head, but how you spontaneously enthral whole congress dinners to sing Finnish folk songs is truly beyond my comprehension.

I want to thank all my co-authors for your help in data wrangling, providing insightful comments, and for catching all the slips that wold have left me embarrassed had they arrived to the editor. Thank you Johan Eriksson, Kati Heinonen, Marjo-Riitta Järvelin, Anna-Liisa Järvenpää, Jari Lahti, Aulikki Lano, Hanna-Maria Matinolli, Markku Nurhonen, Juulia Paavonen, Katri Räikkönen, Marika Sipola-Leppänen, Marjaana Tikanmäki, Marja Vääräsmäki, and Dieter Wolke. A special thank you go to my partners in crime Juho and Liisa Kuula; the recent collaboration with you has felt effortless.

Thank you to my friends from the “office”: Hanna, Julia, Maija, Maiju, Minna, Mira, Peija, Pieta, Risto, Samuel, Sara, and Suvi. You have all either aided my work or provided acute psychotherapy when my brain has started to boil over. I also want to thank congress co-travelers, with a special shout-out to the Psycho team; work trips don’t feel like work when you’re around. And thank you all my much-neglected friends, hopefully I’ll have more time to see you now. I want to thank my parents-in-law for all their babysitting and help in keeping our household running while I’ve been holed up in my office.

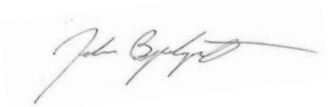
This work wouldn’t exist were it not for the institutions, research assistants, and thousands of subjects who have either laid down their finances or time in the noble cause of advancing science. I thank the following institutions and foundations for financially supporting my personal work: The Doctoral Programme in Clinical Research, The Finnish Institute for Health and Welfare, Finska Läkaresällskapet, and Lastentautien Tutkimussäätiö.

I want to thank my pre-examiners Christian Benedict and Päivi Korhonen. By choice I wrote the summary somewhat *sub rosa* and revealed it to my supervisors when it was quite finished. This means that I spent many hours in front of my computer doubting myself, hoping that I portrayed the science truthfully, my results clearly, and my conclusions justifiably. I audibly let a sigh of relief when you agreed to be my pre-examiners, because I knew that if such experts would scrutinize my book, it would stand on firm ground.

Professor Susan Redline, I wish to extend you my sincere gratitude for agreeing to be my opponent. Your authority in many sleep research questions make you an ideal opponent for many PhD candidates, but your expertise in my exact field make you invaluable to me. I couldn’t have hoped for a more qualified opponent, because I don’t think one exists.

Finally, I want to thank my wife and daughter. This part feels the hardest, because I know that every evening or weekend hour that I have worked has been away from our time together. Especially during the last months of this writing I know you have sacrificed much for me. Bianca, I adore you, and I thank you. Aina, my darling strong-headed girl, you are like sunshine. And you, my son, still in your mother’s womb as I’m writing this, I can’t wait to meet you.

I began at the beginning, and now I have come the end, so here I’ll stop.



Helsinki, March 2019

9. References

Abel T, Havekes R, Saletin JM, Walker MP. 2013. Sleep, Plasticity and Memory from Molecules to Whole-Brain Networks. Curr Biol. 23(17):R774–R788. doi:10.1016/j.cub.2013.07.025.

Adan A, Almirall H. 1991. Horne & Östberg morningness-eveningness questionnaire: A reduced scale. Personal Individ Differ. 12(3):241–253. doi:10.1016/0191-8869(91)90110-W.

Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C. 2012. Circadian Typology: A Comprehensive Review. Chronobiol Int. 29(9):1153–1175. doi:10.3109/07420528.2012.719971.

Akashi M, Soma H, Yamamoto Takuro, Tsugitomi A, Yamashita S, Yamamoto Takuya, Nishida E, Yasuda A, Liao JK, Node K. 2010. Noninvasive method for assessing the human circadian clock using hair follicle cells. Proc Natl Acad Sci. 107(35):15643–15648. doi:10.1073/pnas.1003878107.

Alanne S, Roine RP, Räsänen P, Vainiola T, Sintonen H. 2015. Estimating the minimum important change in the 15D scores. Qual Life Res. 24(3):599–606. doi:10.1007/s11136-014-0787-4.

Albrecht GL, Devlieger PJ. 1999. The disability paradox: high quality of life against all odds. Soc Sci Med. 48(8):977–988. doi:10.1016/S0277-9536(98)00411-0.

Allebrandt KV, Amin N, Müller-Myhsok B, Esko T, Teder-Laving M, Azevedo RVDM, Hayward C, van Mill J, Vogelzangs N, Green EW, et al. 2013. A K_{ATP} channel gene effect on sleep duration: from genome-wide association studies to function in *Drosophila*. Mol Psychiatry. 18(1):122–132. doi:10.1038/mp.2011.142.

Allen GC, Farnell YZ, Maeng J, West JR, Chen W-JA, Earnest DJ. 2005. Long-term effects of neonatal alcohol exposure on photic reentrainment and phase-shifting responses of the activity rhythm in adult rats. Alcohol. 37(2):79–88. doi:10.1016/j.alcohol.2005.11.003.

Allen GC, West JR, Chen W-JA, Earnest DJ. 2005. Neonatal Alcohol Exposure Permanently Disrupts the Circadian Properties and Photic Entrainment of the Activity Rhythm in Adult Rats. Alcohol Clin Exp Res. 29(10):1845–1852. doi:10.1097/01.alc.0000183014.12359.9f.

American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Committee on Obstetric Practice. 1997. Guidelines for perinatal care. 4th ed. Elk Grove Village, IL : American Academy of Pediatrics ; Washington, DC : American College of Obstetricians and Gynecologists, ©1997.

Anafi RC, Kayser MS, Raizen DM. 2019. Exploring phylogeny to find the function of sleep. Nat Rev Neurosci. 20(2):109–116. doi:10.1038/s41583-018-0098-9.

Anothaisintawee T, Lertrattananon D, Thamakaison S, Knutson KL, Thakkinstian A, Reutrakul S. 2017. Later chronotype is associated with higher hemoglobin A1c in prediabetes patients. Chronobiol Int. 34(3):393–402. doi:10.1080/07420528.2017.1279624.

Antonini SR, Jorge SM, Moreira AC. 2000. The emergence of salivary cortisol circadian rhythm and its relationship to sleep activity in preterm infants. Clin Endocrinol (Oxf). 52(4):423–426.

Antypa N, Verkuil B, Molendijk M, Schoevers R, Penninx BWJH, Does WVD. 2017. Associations between chronotypes and psychological vulnerability factors of depression. Chronobiol Int. 34(8):1125–1135. doi:10.1080/07420528.2017.1345932.

Ariagno RL, Mirmiran M. 2001. Shedding light on the very low birth weight infant. J Pediatr. 139(4):476–477. doi:10.1067/mpd.2001.118879.

Arnulf I, Buda C, Sastre J-P. 2018. Michel Jouvet: an explorer of dreams and a great storyteller. Sleep Med. 49:4–9. doi:10.1016/j.sleep.2018.05.033.

Asaka Y, Takada S. 2010. Activity-based assessment of the sleep behaviors of VLBW preterm infants and full-term infants at around 12 months of age. Brain Dev. 32(2):150–155. doi:10.1016/j.braindev.2008.12.006.

Asaka Y, Takada S. 2011. Comparing sleep measures of infants derived from parental reports in sleep diaries and acceleration sensors. Acta Paediatr. 100(8):1158–1163. doi:10.1111/j.1651-2227.2011.02204.x.

Aserinsky E, Kleitman N. 1953. Regularly Occurring Periods of Eye Motility, and Concomitant Phenomena, During Sleep. Science. 118(3062):273–274. doi:10.1126/science.118.3062.273.

Asher G, Sassone-Corsi P. 2015. Time for Food: The Intimate Interplay between Nutrition, Metabolism, and the Circadian Clock. Cell. 161(1):84–92. doi:10.1016/j.cell.2015.03.015.

Au J, Reece J. 2017. The relationship between chronotype and depressive symptoms: A meta-analysis. J Affect Disord. 218:93–104. doi:10.1016/j.jad.2017.04.021.

Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. 2015. Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015. J Clin Sleep Med. 11(10):1199–1236. doi:10.5664/jcsm.5100.

Baehr EK, Revelle W, Eastman CI. 2000. Individual differences in the phase and amplitude of the human circadian temperature rhythm: with an emphasis on morningness–eveningness. J Sleep Res. 9(2):117–127. doi:10.1046/j.1365-2869.2000.00196.x.

Bailey SL, Heitkemper MM. 2001. Circadian Rhythmicity of Cortisol and Body

Temperature: Morningness-Eveningness Effects. Chronobiol Int. 18(2):249–261. doi:10.1081/CBI-100103189.

Barclay NL, Eley TC, Buysse DJ, Archer SN, Gregory AM. 2010. Diurnal preference and sleep quality: same genes? A study of young adult twins. Chronobiol Int. 27(2):278–296. doi:10.3109/07420521003663801.

Barker DJP. 2007. The origins of the developmental origins theory. J Intern Med. 261(5):412–417. doi:10.1111/j.1365-2796.2007.01809.x.

Barker DJP, Osmond C, Winter PD, Margetts B, Simmonds SJ. 1989. Weight in infancy and death from iscaemic heart disease. The Lancet. 334(8663):577–580. doi:10.1016/S0140-6736(89)90710-1.

Basnet S, Merikanto I, Lahti T, Männistö S, Laatikainen T, Vartiainen E, Partonen T. 2017. Associations of common noncommunicable medical conditions and chronic diseases with chronotype in a population-based health examination study. Chronobiol Int. 34(4):462–470. doi:10.1080/07420528.2017.1295050.

Basnet S, Merikanto I, Lahti T, Männistö S, Laatikainen T, Vartiainen E, Partonen T. 2018. Seasonality, morningness-eveningness, and sleep in common non - communicable medical conditions and chronic diseases in a population. Sleep Sci. 11(2). doi:10.5935/1984-0063.20180017.

Båtsvik B, Vederhus BJ, Halvorsen T, Wentzel-Larsen T, Graue M, Markestad T. 2015. Health-related quality of life may deteriorate from adolescence to young adulthood after extremely preterm birth. Acta Paediatr. 104(9):948–955. doi:10.1111/apa.13069.

Baumann N, Bartmann P, Wolke D. 2016. Health-Related Quality of Life Into Adulthood After Very Preterm Birth. Pediatrics. 137(4):e20153148–e20153148. doi:10.1542/peds.2015-3148.

Baumgardt M, Bucher HU, Arlettaz Mieth R, Fauchère J-C. 2012. Health-related quality of life of former very preterm infants in adulthood: Adult HRQOL in former VLBW infants. Acta Paediatr. 101(2):e59–e63. doi:10.1111/j.1651-2227.2011.02422.x.

Beaudoin S, Tremblay GM, Croitoru D, Benedetti A, Landry JS. 2013. Healthcare utilization and health-related quality of life of adult survivors of preterm birth complicated by bronchopulmonary dysplasia. Acta Paediatr. 102(6):607–612. doi:10.1111/apa.12217.

Becker K, Steinberg H, Kluge M. 2016. Emil Kraepelin's concepts of the phenomenology and physiology of sleep: The first systematic description of chronotypes. Sleep Med Rev. 27:9–19. doi:10.1016/j.smrv.2015.06.001.

Bellavia S, Carpentieri A, Vaque A, Macchione A, Vermouth N. 2006. Pup circadian rhythm entrainment—effect of maternal ganglionectomy or pinealectomy. Physiol Behav. 89(3):342–349. doi:10.1016/j.physbeh.2006.06.018.

Bhadra U, Thakkar N, Das P, Pal Bhadra M. 2017. Evolution of circadian rhythms: from bacteria to human. Sleep Med. 35:49–61. doi:10.1016/j.sleep.2017.04.008.

Bhattacharya Sohinee, Raja EA, Mirazo ER, Campbell DM, Lee AJ, Norman JE, Bhattacharya Siladitya. 2010. Inherited predisposition to spontaneous preterm delivery. Obstet Gynecol. 115(6):1125–1133.

Bilgin A, Mendonca M, Wolke D. 2018. Preterm Birth/Low Birth Weight and Markers Reflective of Wealth in Adulthood: A Meta-analysis. Pediatrics. 142(1):e20173625. doi:10.1542/peds.2017-3625.

Bin YS, Marshall NS, Glozier N. 2012. Secular trends in adult sleep duration: A systematic review. Sleep Med Rev. 16(3):223–230. doi:10.1016/j.smrv.2011.07.003.

Bin YS, Marshall NS, Glozier N. 2013. Sleeping at the limits: the changing prevalence of short and long sleep durations in 10 countries. Am J Epidemiol. 177(8):826–833. doi:10.1093/aje/kws308.

Bjerager M, Steensberg J, Greisen G. 1995. Quality of life among young adults born with very low birth weights. Acta Paediatr. 84(12):1339–1343.

Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, Adler A, Garcia CV, Rohde S, Say L. 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. The Lancet. 379(9832):2162–2172.

Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. 2013. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 74(Suppl 1):35–49. doi:10.1038/pr.2013.205.

Borbély AA. 1982. A two process model of sleep regulation. Hum Neurobiol. 1(3):195–204.

Borbély AA, Daan S, Wirz-Justice A, Deboer T. 2016. The two-process model of sleep regulation: a reappraisal. J Sleep Res. 25(2):131–143. doi:10.1111/jsr.12371.

de Bourrienne LAF, Phipps RW. 1829. Memoirs of Napoleon Bonaparte, Complete. [accessed 2019 Jan 10]. https://www.gutenberg.org/files/3567/3567-h/3567-h.htm.

Boyd HA, Poulsen G, Wohlfahrt J, Murray JC, Feenstra B, Melbye M. 2009. Maternal Contributions to Preterm Delivery. Am J Epidemiol. 170(11):1358–1364. doi:10.1093/aje/kwp324.

Breeman LD, Jaekel J, Baumann N, Bartmann P, Wolke D. 2015. Preterm Cognitive Function Into Adulthood. Pediatrics. 136(3):415–423. doi:10.1542/peds.2015-0608.

Brooks E, Patel D, Canal MM. 2014. Programming of Mice Circadian Photic Responses

by Postnatal Light Environment. PLOS ONE. 9(5):e97160. doi:10.1371/journal.pone.0097160.

Brooks E, Waters E, Farrington L, Canal MM. 2011. Differential hypothalamic tyrosine hydroxylase distribution and activation by light in adult mice reared under different light conditions during the suckling period. Brain Struct Funct. 216(4):357–370. doi:10.1007/s00429-011-0318-9.

Brown SA, Azzi A. 2013. Peripheral Circadian Oscillators in Mammals. In: Kramer A, Merrow M, editors. Circadian Clocks. Berlin, Heidelberg: Springer Berlin Heidelberg. (Handbook of Experimental Pharmacology). p. 45–66. https://doi.org/10.1007/978-3-642-25950-0_3.

Bueno C, Menna-Barreto L. 2016. Development of sleep/wake, activity and temperature rhythms in newborns maintained in a neonatal intensive care unit and the impact of feeding schedules. Infant Behav Dev. 44:21–28. doi:10.1016/j.infbeh.2016.05.004.

Burgess HJ, Savic N, Sletten T, Roach G, Gilbert SS, Dawson D. 2003. The Relationship Between the Dim Light Melatonin Onset and Sleep on a Regular Schedule in Young Healthy Adults. Behav Sleep Med. 1(2):102–114. doi:10.1207/S15402010BSM0102_3.

Canal MM, Mohammed NM, Rodríguez JJ. 2009. Early programming of astrocyte organization in the mouse suprachiasmatic nuclei by light. Chronobiol Int. 26(8):1545–1558. doi:10.3109/07420520903398542.

Canal-Corretger MM, Cambras T, Vilaplana J, Díez-Noguera A. 2000. Bright light during lactation alters the functioning of the circadian system of adult rats. Am J Physiol-Regul Integr Comp Physiol. 278(1):R201–R208. doi:10.1152/ajpregu.2000.278.1.R201.

Canal-Corretger MM, Vilaplana J, Cambras T, Díez-Noguera A. 2001. Effect of light on the development of the circadian rhythm of motor activity in the mouse. Chronobiol Int. 18(4):683–696. doi:10.1081/CBI-100106081.

Caravale B, Sette S, Cannoni E, Marano A, Riolo E, Devescovi A, De Curtis M, Bruni O. 2017. Sleep Characteristics and Temperament in Preterm Children at Two Years of Age. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 13(9):1081–1088. doi:10.5664/jcsm.6728.

Challet E, Poirel V-J, Malan A, Pévet P. 2003. Light exposure during daytime modulates expression of Per1 and Per2 clock genes in the suprachiasmatic nuclei of mice. J Neurosci Res. 72(5):629–637. doi:10.1002/jnr.10616.

Chan JWY, Lam SP, Li SX, Yu MWM, Chan NY, Zhang J, Wing Y-K. 2014. Eveningness and Insomnia: Independent Risk Factors of Nonremission in Major Depressive Disorder. Sleep. 37(5):911–917. doi:10.5665/sleep.3658.

Chaput J-P, Dutil C, Sampasa-Kanyinga H. 2018. Sleeping hours: what is the ideal number and how does age impact this? Nat Sci Sleep. 10:421–430. doi:10.2147/NSS.S163071.

Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, Landoulsi S, Jampathong N, Kongwattanakul K, Laopaiboon M, et al. 2019. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health. 7(1):e37–e46. doi:10.1016/S2214-109X(18)30451-0.

Ciarleglio CM, Axley JC, Strauss BR, Gamble KL, McMahon DG. 2011. Perinatal photoperiod imprints the circadian clock. Nat Neurosci. 14(1):25–27. doi:10.1038/nn.2699.

Cirelli C, Tononi G. 2008. Is Sleep Essential? PLoS Biol. 6(8):e216. doi:10.1371/journal.pbio.0060216.

Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. 2007. Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endocrinol Metab. 92(3):804–810. doi:10.1210/jc.2006-2017.

Cnattingius S, Villamor E, Johansson S, Bonamy A-KE, Persson M, Wikström A-K, Granath F. 2013. Maternal obesity and risk of preterm delivery. JAMA. 309(22):2362–2370.

Coogan AN, McGowan NM. 2017. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. ADHD Atten Deficit Hyperact Disord. 9(3):129–147. doi:10.1007/s12402-016-0214-5.

Cooke RWI. 2004. Health, lifestyle, and quality of life for young adults born very preterm. Arch Dis Child. 89(3):201–206. doi:10.1136/adc.2003.030197.

Cordina-Duverger E, Menegaux F, Popa A, Rabstein S, Harth V, Pesch B, Brüning T, Fritschi L, Glass DC, Heyworth JS, et al. 2018. Night shift work and breast cancer: a pooled analysis of population-based case–control studies with complete work history. Eur J Epidemiol. 33(4):369–379. doi:10.1007/s10654-018-0368-x.

Crossland RF, Balasa A, Ramakrishnan R, Mahadevan SK, Fiorotto ML, Van den Veyver IB. 2017. Chronic Maternal Low-Protein Diet in Mice Affects Anxiety, Night-Time Energy Expenditure and Sleep Patterns, but Not Circadian Rhythm in Male Offspring. PLOS ONE. 12(1):e0170127. doi:10.1371/journal.pone.0170127.

Crump C, Friberg D, Li X, Sundquist J, Sundquist K. 2019. Preterm birth and risk of sleep-disordered breathing from childhood into mid-adulthood. Int J Epidemiol. doi:10.1093/ije/dyz075.

Crump C, Winkleby MA, Sundquist K, Sundquist J. 2011. Risk of Diabetes Among Young Adults Born Preterm in Sweden. Diabetes Care. 34(5):1109–1113. doi:10.2337/dc10-2108.

Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, Harding JE. 2007. Psychological functioning and health-related quality

of life in adulthood after preterm birth. Dev Med Child Neurol. 49(8):597–602.

Darlow BA, Horwood LJ, Pere-Bracken HM, Woodward LJ. 2013. Psychosocial Outcomes of Young Adults Born Very Low Birth Weight. Pediatrics. 132(6):e1521–e1528. doi:10.1542/peds.2013-2024.

Dashti HS, Jones SE, Wood AR, Lane JM, Hees VT van, Wang H, Rhodes JA, Song Y, Patel K, Anderson SG, et al. 2019. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. Nat Commun. 10(1):1100. doi:10.1038/s41467-019-08917-4.

de Jong F, Monuteaux MC., van Elburg RM., Gillman MW., Belfort MB. 2012. Systematic Review and Meta-Analysis of Preterm Birth and Later Systolic Blood Pressure. Hypertension. 59(2):226–234. doi:10.1161/HYPERTENSIONAHA.111.181784.

DeMauro SB, Dysart K, Kirpalani H. 2014. Stopping the Swinging Pendulum of Postnatal Corticosteroid Use. J Pediatr. 164(1):9–11. doi:10.1016/j.jpeds.2013.10.020.

Dimitrov A, Veer IM, Kleeblatt J, Seyfarth F, Roenneberg T, Ising M, Uhr M, Keck ME, Kramer A, Berger M, et al. 2018. Chronotype is associated with psychological well-being depending on the composition of the study sample. J Health Psychol.:1–12. doi:10.1177/1359105317751618.

Dinesen S, Greisen G. 2001. Quality of life in young adults with very low birth weight. Arch Dis Child - Fetal Neonatal Ed. 85:F165–F169.

D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. 2013. Preterm Birth and Mortality and Morbidity: A Population-Based Quasi-experimental Study. JAMA Psychiatry. 70(11):1231–1240. doi:10.1001/jamapsychiatry.2013.2107.

Doyle LW, Andersson S, Bush A, Cheong JLY, Clemm H, Evensen KAI, Gough A, Halvorsen T, Hovi P, Kajantie E, et al. 2019. Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls born at term or with normal birthweight: a meta-analysis of individual participant data. Lancet Respir Med. 7(8):677–686. doi:10.1016/S2213-2600(18)30530-7.

Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. 2014. An Update on the Impact of Postnatal Systemic Corticosteroids on Mortality and Cerebral Palsy in Preterm Infants: Effect Modification by Risk of Bronchopulmonary Dysplasia. J Pediatr. 165(6):1258–1260. doi:10.1016/j.jpeds.2014.07.049.

Driller MW, O'Donnell S, Tavares F. 2017. What wrist should you wear your actigraphy device on? Analysis of dominant vs. non-dominant wrist actigraphy for measuring sleep in healthy adults. Sleep Sci. 10(3):132–135. doi:10.5935/1984-0063.20170023.

Dubowy C, Moravcevic K, Yue Z, Wan JY, Van Dongen HPA, Sehgal A. 2016. Genetic Dissociation of Daily Sleep and Sleep Following Thermogenetic Sleep Deprivation in Drosophila. Sleep. 39(5):1083–1095. doi:10.5665/sleep.5760.

Duffy JF, Cain SW, Chang A-M, Phillips AJK, Münch MY, Gronfier C, Wyatt JK, Dijk D-J, Wright KP, Czeisler CA. 2011. Sex difference in the near-24-hour intrinsic period of the human circadian timing system. Proc Natl Acad Sci. 108(Supplement 3):15602–15608. doi:10.1073/pnas.1010666108.

Duffy JF, Dijk DJ, Hall EF, Czeisler CA. 1999. Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. J Investig Med Off Publ Am Fed Clin Res. 47(3):141–150.

Duffy JF, Rimmer DW, Czeisler CA. 2001. Association of Intrinsic Circadian Period With Morningness-Eveningness, Usual Wake Time, and Circadian Phase. Behav Neurosci. 115(4):895–899.

Duggan KA, Friedman HS, McDevitt EA, Mednick SC. 2014. Personality and Healthy Sleep: The Importance of Conscientiousness and Neuroticism. PLoS ONE. 9(3):e90628. doi:10.1371/journal.pone.0090628.

Dunster GP, Iglesia L de la, Ben-Hamo M, Nave C, Fleischer JG, Panda S, Iglesia HO de la. 2018. Sleepmore in Seattle: Later school start times are associated with more sleep and better performance in high school students. Sci Adv. 4(12):eaau6200. doi:10.1126/sciadv.aau6200.

Dunsworth HM. 2018. There Is No "Obstetrical Dilemma": Towards a Braver Medicine with Fewer Childbirth Interventions. Perspect Biol Med. 61(2):249–263. doi:10.1353/pbm.2018.0040.

Dunsworth HM, Warrener AG, Deacon T, Ellison PT, Pontzer H. 2012. Metabolic hypothesis for human altriciality. Proc Natl Acad Sci. 109(38):15212–15216. doi:10.1073/pnas.1205282109.

Durán P, Cintra L, Galler JR, Tonkiss J. 2005. Prenatal protein malnutrition induces a phase shift advance of the spontaneous locomotor rhythm and alters the rest/activity ratio in adult rats. Nutr Neurosci. 8(3):167–172. doi:10.1080/10284150400026117.

Edgar RS, Green EW, Zhao Y, Ooijen G van, Olmedo M, Qin X, Xu Y, Pan M, Valekunja UK, Feeney KA, et al. 2012. Peroxiredoxins are conserved markers of circadian rhythms. Nature. 485(7399):459–464. doi:10.1038/nature11088.

Ehlen JC, Brager AJ, Baggs J, Pinckney L, Gray CL, DeBruyne JP, Esser KA, Takahashi JS, Paul KN. 2017. Bmal1 function in skeletal muscle regulates sleep. eLife. 6:e26557. doi:10.7554/eLife.26557.

Engle WA, Tomashek KM, Wallman C, and the Committee on Fetus and Newborn. 2007. "Late-Preterm" Infants: A Population at Risk. Pediatrics. 120(6):1390–1401. doi:10.1542/peds.2007-2952.

Eryigit-Madzwamuse S, Strauss V, Baumann N, Bartmann P, Wolke D. 2015. Personality of adults who were born very preterm. Arch Dis Child - Fetal Neonatal Ed. 100(6):F524–F529. doi:10.1136/archdischild-2014-308007.

eurofound.europa.eu. How many times a month do you work at night? [accessed 2018 Dec 29]. https://www.eurofound.europa.eu/data/european-working-conditions-survey.

Farnell YZ, Allen GC, Nahm S-S, Neuendorff N, West JR, Chen W-JA, Earnest DJ. 2008. Neonatal Alcohol Exposure Differentially Alters Clock Gene Oscillations Within the Suprachiasmatic Nucleus, Cerebellum, and Liver of Adult Rats. Alcohol Clin Exp Res. 32(3):544–552. doi:10.1111/j.1530-0277.2007.00598.x.

Farnell YZ, West JR, Chen W-JA, Allen GC, Earnest DJ. 2004. Developmental Alcohol Exposure Alters Light-Induced Phase Shifts of the Circadian Activity Rhythm in Rats. Alcohol Clin Exp Res. 28(7):1020–1027. doi:10.1097/01.ALC.0000130807.21020.1B.

Faul F, Erdfelder E, Lang A-G, Buchner A. 2007. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 39(2):175–191. doi:10.3758/BF03193146.

Flensborg-Madsen T, Mortensen EL. 2017. Birth Weight and Intelligence in Young Adulthood and Midlife. Pediatrics. 139(6):e20163161. doi:10.1542/peds.2016-3161.

Gäddlin P-O, Finnström O, Sydsjö G, Leijon I. 2009. Most very low birth weight subjects do well as adults. Acta Paediatr. 98(9):1513–1520. doi:10.1111/j.1651-2227.2009.01368.x.

Gershon A, Kaufmann CN, Depp CA, Miller S, Do D, Zeitzer JM, Ketter TA. 2018. Subjective versus objective evening chronotypes in bipolar disorder. J Affect Disord. 225:342–349. doi:10.1016/j.jad.2017.08.055.

Giampietro M, Cavallera GM. 2007. Morning and evening types and creative thinking. Personal Individ Differ. 42(3):453–463. doi:10.1016/j.paid.2006.06.027.

Gluckman PD, Hanson MA, Spencer HG. 2005. Predictive adaptive responses and human evolution. Trends Ecol Evol. 20(10):527–533. doi:10.1016/j.tree.2005.08.001.

Goldenberg RL, Culhane JF, Iams JD, Romero R. 2008. Epidemiology and causes of preterm birth. The Lancet. 371(9606):75–84. doi:10.1016/S0140-6736(08)60074-4.

Goldenberg RL, Hauth JC, Andrews WW. 2000. Intrauterine infection and preterm delivery. N Engl J Med. 342(20):1500–1507.

Gössel-Symank R, Grimmer I, Korte J, Siegmund R. 2004. Actigraphic Monitoring of the Activity-Rest Behavior of Preterm and Full-Term Infants at 20 Months of Age. Chronobiol Int. 21(4–5):661–671. doi:10.1081/CBI-120039208.

Gottlieb DJ, O'Connor GT, Wilk JB. 2007. Genome-wide association of sleep and circadian phenotypes. BMC Med Genet. 8(Suppl 1):S9. doi:10.1186/1471-2350-8-S1-S9.

Griefahn B. 2002. The validity of the temporal parameters of the daily rhythm of melatonin levels as an indicator of morningness. Chronobiol Int. 19(3):561–577. doi:10.1081/CBI-120004226.

Guyer C, Huber R, Fontijn J, Bucher HU, Nicolai H, Werner H, Molinari L, Latal B, Jenni OG. 2015. Very preterm infants show earlier emergence of 24-hour sleep–wake rhythms compared to term infants. Early Hum Dev. 91(1):37–42. doi:10.1016/j.earlhumdev.2014.11.002.

Hack M. 2009. Adult outcomes of preterm children. J Dev Behav Pediatr. 30(5):460–470.

Hagmann-von Arx P, Perkinson-Gloor N, Brand S, Albert D, Holsboer-Trachsler E, Grob A, Weber P, Lemola S. 2014. In School-Age Children Who Were Born Very Preterm Sleep Efficiency Is Associated with Cognitive Function. Neuropsychobiology. 70(4):244–252. doi:10.1159/000369026.

Handa RJ, Zuloaga DG, McGivern RF. 2007. Prenatal ethanol exposure alters core body temperature and corticosterone rhythms in adult male rats. Alcohol. 41(8):567–575. doi:10.1016/j.alcohol.2007.09.004.

Hao H, Rivkees SA. 1999. The biological clock of very premature primate infants is responsive to light. Proc Natl Acad Sci. 96(5):2426–2429. doi:10.1073/pnas.96.5.2426.

Haraden DA, Mullin BC, Hankin BL. 2017. The relationship between depression and chronotype: A longitudinal assessment during childhood and adolescence. Depress Anxiety. 34(10):967–976. doi:10.1002/da.22682.

He Y, Jones CR, Fujiki N, Xu Y, Guo B, Holder JL, Rossner MJ, Nishino S, Fu Y-H. 2009. The Transcriptional Repressor DEC2 Regulates Sleep Length in Mammals. Science. 325(5942):866–870. doi:10.1126/science.1174443.

Heath AC, Kendler KS, Eaves LJ, Martin NG. 1990. Evidence for Genetic Influences on Sleep Disturbance and Sleep Pattern in Twins. Sleep. 13(4):318–335. doi:10.1093/sleep/13.4.318.

Heinonen K, Räikkonen K, Pesonen A-K, Kajantie E, Andersson S, Eriksson JG, Niemelä A, Vartia T, Peltola J, Lano A. 2008. Prenatal and Postnatal Growth and Cognitive Abilities at 56 Months of Age: A Longitudinal Study of Infants Born at Term. Pediatrics. 121(5):e1325–e1333. doi:10.1542/peds.2007-1172.

Helenius K, Sjörs G, Shah PS, Modi N, Reichman B, Morisaki N, Kusuda S, Lui K, Darlow BA, Bassler D, et al. 2017. Survival in Very Preterm Infants: An International Comparison of 10 National Neonatal Networks. Pediatrics. 140(6):e20171264. doi:10.1542/peds.2017-1264.

Hertz CL, Mathiasen R, Hansen BM, Mortensen EL, Greisen G. 2013. Personality in Adults Who Were Born Very Preterm. PLOS ONE. 8(6):e66881. doi:10.1371/journal.pone.0066881.

Hibbs AM, Muhlebach M. 2017. Respiratory outcomes in preterm infants. New York, NY: Springer Science+Business Media, LLC.

Hibbs AM, Storfer-Isser A, Rosen C, Ievers-Landis CE, Taveras EM, Redline S. 2014. Advanced Sleep Phase in Adolescents Born Preterm. Behav Sleep Med. 12(5):412–424. doi:10.1080/15402002.2013.825838.

Hilaire MAS, Gooley JJ, Khalsa SBS, Kronauer RE, Czeisler CA, Lockley SW. 2012. Human phase response curve to a 1 h pulse of bright white light. J Physiol. 590(13):3035–3045. doi:10.1113/jphysiol.2012.227892.

Hines D, Modi N, Lee SK, Isayama T, Sjörs G, Gagliardi L, Lehtonen L, Vento M, Kusuda S, Bassler D, et al. 2017. Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus. Acta Paediatr. 106(3):366–374. doi:10.1111/apa.13672.

Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Adams Hillard PJ, Katz ES, et al. 2015. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health. 1(4):233–243. doi:10.1016/j.sleh.2015.10.004.

Hisler GC, Phillips AL, Krizan Z. 2017. Individual Differences in Diurnal Preference and Time-of-Exercise Interact to Predict Exercise Frequency. Ann Behav Med. 51(3):391–401. doi:10.1007/s12160-016-9862-0.

Hoenig JM, Heisey DM. 2001. The Abuse of Power: The Pervasive Fallacy of Power Calculations for Data Analysis. Am Stat. 55(1):19–24. doi:10.1198/000313001300339897.

Horbar JD, Badger GJ, Carpenter JH, Fanaroff AA, Kilpatrick S, LaCorte M, Phibbs R, Soll RF. 2002. Trends in Mortality and Morbidity for Very Low Birth Weight Infants, 1991–1999. Pediatrics. 110(1):143–151. doi:10.1542/peds.110.1.143.

Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, Buzas JS. 2012. Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009. Pediatrics. 129(6):1019–1026. doi:10.1542/peds.2011-3028.

Horne JA, Östberg O. 1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 4(2):97–110.

Horne JA, Östberg O. 1977. Individual differences in human circadian rhythms. Biol Psychol. 5(3):179–190. doi:10.1016/0301-0511(77)90001-1.

Hovi P, Andersson S, Eriksson JG, Järvenpää A-L, Strang-Karlsson S, Mäkitie O, Kajantie E. 2007. Glucose regulation in young adults with very low birth weight. N Engl J Med. 356(20):2053–2063.

Hovi P, Vohr B, Ment LR, Doyle LW, McGarvey L, Morrison KM, Evensen KAI, van der Pal S, Grunau RE, Brubakk A-M. 2016. Blood pressure in young adults born at very low birth weight. Hypertension. 68:880–887. doi:10.1161/HYPERTENSIONAHA.116.08167.

Hower IM, Harper SA, Buford TW. 2018. Circadian Rhythms, Exercise, and Cardiovascular Health. J Circadian Rhythms. 16(1):1-8. doi:10.5334/jcr.164.

Hu Y, Shmygelska A, Tran D, Eriksson N, Tung JY, Hinds DA. 2016. GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. Nat Commun. 7:10448. doi:10.1038/ncomms10448.

Huang Y-S, Paiva T, Hsu J-F, Kuo M-C, Guilleminault C. 2014. Sleep and breathing in premature infants at 6 months post-natal age. BMC Pediatr. 14(1):303.

Hur Y-M, Bouchard Jr. TJ, Lykken DT. 1998. Genetic and environmental influence on morningness–eveningness. Personal Individ Differ. 25(5):917–925. doi:10.1016/S0191-8869(98)00089-0.

Husby IM, Stray KM-T, Olsen A, Lydersen S, Indredavik MS, Brubakk A-M, Skranes J, Evensen KAI. 2016. Long-term follow-up of mental health, health-related quality of life and associations with motor skills in young adults born preterm with very low birth weight. Health Qual Life Outcomes. 14(1). doi:10.1186/s12955-016-0458-y.

Iglowstein I, Latal Hajnal B, Molinari L, Largo R, Jenni O. 2006. Sleep behaviour in preterm children from birth to age 10 years: A longitudinal study. Acta Paediatr. 95(12):1691–1693. doi:10.1080/08035250600686938.

Inderkum AP, Tarokh L. 2018. High heritability of adolescent sleep–wake behavior on free, but not school days: a long-term twin study. Sleep. 41(3). doi:10.1093/sleep/zsy004.

Ion R, Bernal AL. 2015. Smoking and Preterm Birth. Reprod Sci. 22(8):918–926. doi:10.1177/1933719114556486.

Itani O, Jike M, Watanabe N, Kaneita Y. 2017. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. Sleep Med. 32:246–256. doi:10.1016/j.sleep.2016.08.006.

Ivars K, Nelson N, Theodorsson A, Theodorsson E, Ström JO, Mörelius E. 2015. Development of Salivary Cortisol Circadian Rhythm and Reference Intervals in Full-Term Infants. PLOS ONE. 10(6):e0129502. doi:10.1371/journal.pone.0129502.

Ivars K, Nelson N, Theodorsson A, Theodorsson E, Ström JO, Mörelius E. 2017. Development of salivary cortisol circadian rhythm in preterm infants. PLOS ONE. 12(8):e0182685. doi:10.1371/journal.pone.0182685.

Jaekel J, Baumann N, Bartmann P, Wolke D. 2018. Mood and anxiety disorders in very preterm/very low-birth weight individuals from 6 to 26 years. J Child Psychol Psychiatry. 59(1):88–95. doi:10.1111/jcpp.12787.

Jan JE, Wasdell MB, Freeman RD, Bax M. 2007. Evidence supporting the use of melatonin in short gestation infants. J Pineal Res. 42(1):22–27. doi:10.1111/j.1600-079X.2006.00398.x.

Järvenpää AL, Granström ML. 1987. [The development, social behavior and prognosis of premature infants]. Duodecim Lääketieteellinen Aikakauskirja. 103(20):1238–1246.

Jones SE, Lane JM, Wood AR, Hees VT van, Tyrrell J, Beaumont RN, Jeffries AR, Dashti HS, Hillsdon M, Ruth KS, et al. 2019. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. Nat Commun. 10(1):343. doi:10.1038/s41467-018-08259-7.

Jones SE, Tyrrell J, Wood AR, Beaumont RN, Ruth KS, Tuke MA, Yaghootkar H, Hu Y, Teder-Laving M, Hayward C, et al. 2016. Genome-Wide Association Analyses in 128,266 Individuals Identifies New Morningness and Sleep Duration Loci. PLOS Genet. 12(8):e1006125. doi:10.1371/journal.pgen.1006125.

Joseph D, Chong NW, Shanks ME, Rosato E, Taub NA, Petersen SA, Symonds ME, Whitehouse WP, Wailoo M. 2015. Getting rhythm: how do babies do it? Arch Dis Child - Fetal Neonatal Ed. 100(1):F50–F54. doi:10.1136/archdischild-2014-306104.

Joseph V, Mamet J, Lee F, Dalmaz Y, Van Reeth O. 2002. Prenatal hypoxia impairs circadian synchronisation and response of the biological clock to light in adult rats. J Physiol. 543(1):387–395. doi:10.1113/jphysiol.2002.022236.

Kaijser M, Bonamy A-KE, Akre O, Cnattingius S, Granath F, Norman M, Ekbom A. 2009. Perinatal Risk Factors for Diabetes in Later Life. Diabetes. 58(3):523–526. doi:10.2337/db08-0558.

Kaijser M, Bonamy A-KE, Akre O, Cnattingius S, Granath F, Norman M, Ekbom A. 2008. Perinatal Risk Factors for Ischemic Heart Disease. Circulation. 117(3):405–410. doi:10.1161/CIRCULATIONAHA.107.710715.

Kajantie E, Hovi P. 2014. Is very preterm birth a risk factor for adult cardiometabolic disease? Semin Fetal Neonatal Med. 19(2):112–117. doi:10.1016/j.siny.2013.11.006.

Kajantie E, Hovi P, Räikkonen K, Pesonen A-K, Heinonen K, Järvenpää A-L, Eriksson JG, Strang-Karlsson S, Andersson S. 2008. Young Adults With Very Low Birth Weight: Leaving the Parental Home and Sexual Relationships--Helsinki Study of Very Low Birth Weight Adults. Pediatrics. 122(1):e62–e72. doi:10.1542/peds.2007-3858.

Kajantie E, Osmond C, Barker DJP, Eriksson JG. 2010. Preterm Birth—A Risk Factor for Type 2 Diabetes?: The Helsinki Birth Cohort Study. Diabetes Care. 33(12):2623–2625. doi:10.2337/dc10-0912.

Kajantie E, Osmond C, Eriksson JG. 2015. Coronary Heart Disease and Stroke in Adults Born Preterm – The Helsinki Birth Cohort Study. Paediatr Perinat Epidemiol. 29(6):515–519. doi:10.1111/ppe.12219.

Kajantie E, Strang-Karlsson S, Hovi P, Räikkönen K, Pesonen A-K, Heinonen K, Järvenpää A-L, Eriksson JG, Andersson S. 2010. Adults Born at Very Low Birth Weight Exercise Less than Their Peers Born at Term. J Pediatr. 157(4):610-616.e1. doi:10.1016/j.jpeds.2010.04.002.

Kalmbach DA, Schneider LD, Cheung J, Bertrand SJ, Kariharan T, Pack AI, Gehrman PR. 2017. Genetic Basis of Chronotype in Humans: Insights From Three Landmark GWAS. Sleep. 40(2). doi:10.1093/sleep/zsw048.

Kanazawa S, Perina K. 2009. Why night owls are more intelligent. Personal Individ Differ. 47(7):685–690. doi:10.1016/j.paid.2009.05.021.

Kantermann T, Sung H, Burgess HJ. 2015. Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the Dim Light Melatonin Onset. J Biol Rhythms. 30(5):449–453. doi:10.1177/0748730415597520.

Kaseva N, Martikainen S, Tammelin T, Hovi P, Järvenpää A-L, Andersson S, Eriksson JG, Räikkönen K, Pesonen A-K, Wehkalampi K, et al. 2015. Objectively Measured Physical Activity in Young Adults Born Preterm at Very Low Birth Weight. J Pediatr. 166(2):474–476. doi:10.1016/j.jpeds.2014.10.018.

Kaseva N, Wehkalampi K, Strang-Karlsson S, Salonen M, Pesonen A-K, Räikkönen K, Tammelin T, Hovi P, Lahti J, Heinonen K, et al. 2012. Lower Conditioning Leisure-Time Physical Activity in Young Adults Born Preterm at Very Low Birth Weight. PLOS ONE. 7(2):e32430. doi:10.1371/journal.pone.0032430.

Kawato M, Fujita K, Suzuki R, Winfree AT. 1982. A three-oscillator model of the human circadian system controlling the core temperature rhythm and the sleep-wake cycle. J Theor Biol. 98(3):369–392.

Kazemier B, Buijs P, Mignini L, Limpens J, de Groot C, Mol B, EBM CONNECT. 2014. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG Int J Obstet Gynaecol. 121(10):1197–1208. doi:10.1111/1471-0528.12896.

Kennaway DJ, Goble FC, Stamp GE. 1996. Factors influencing the development of melatonin rhythmicity in humans. J Clin Endocrinol Metab. 81(4):1525–1532. doi:10.1210/jcem.81.4.8636362.

Kennaway DJ, Stamp GE, Goble FC. 1992. Development of melatonin production in infants and the impact of prematurity. J Clin Endocrinol Metab. 75(2):367–369. doi:10.1210/jcem.75.2.1639937.

Kent AL, Wright IMR, Abdel-Latif ME, the New South Wales and Australian Capital Territory

Neonatal Intensive Care Units Audit Group. 2012. Mortality and Adverse Neurologic Outcomes Are Greater in Preterm Male Infants. Pediatrics. 129(1):124–131. doi:10.1542/peds.2011-1578.

Kitamura S, Hida A, Aritake S, Higuchi S, Enomoto M, Kato M, Vetter C, Roenneberg T, Mishima K. 2014. Validity of the Japanese version of the Munich ChronoType Questionnaire. Chronobiol Int. 31(7):845–850. doi:10.3109/07420528.2014.914035.

Kivelä L, Papadopoulos MR, Antypa N. 2018. Chronotype and Psychiatric Disorders. Curr Sleep Med Rep. 4(2):94–103. doi:10.1007/s40675-018-0113-8.

Klei L, Reitz P, Miller M, Wood J, Maendel S, Gross D, Waldner T, Eaton J, Monk TH, Nimgaonkar DVL. 2005. Heritability of Morningness-Eveningness and Self-Report Sleep Measures in a Family-Based Sample of 521 Hutterites. Chronobiol Int. 22(6):1041–1054. doi:10.1080/07420520500397959.

Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE. 2002. Comparisons of the Variability of Three Markers of the Human Circadian Pacemaker. J Biol Rhythms. 17(2):181–193. doi:10.1177/074873002129002474.

Knudsen IR, Bonde JP, Petersen SB. 2018. Physically strenuous work during pregnancy and risk of preterm birth. Arch Environ Occup Health. 73(4):236-242. doi:10.1080/19338244.2017.1342589.

Knutson KL, von Schantz M. 2018. Associations between chronotype, morbidity and mortality in the UK Biobank cohort. Chronobiol Int. 35(8):1045–1053. doi:10.1080/07420528.2018.1454458.

Koehl M, Barbazanges A, Le Moal M, Maccari S. 1997. Prenatal stress induces a phase advance of circadian corticosterone rhythm in adult rats which is prevented by postnatal stress. Brain Res. 759(2):317–320. doi:10.1016/S0006-8993(97)00394-6.

Koehl M, Darnaudéry M, Dulluc J, Reeth OV, Moal ML, Maccari S. 1999. Prenatal stress alters circadian activity of hypothalamo–pituitary–adrenal axis and hippocampal corticosteroid receptors in adult rats of both gender. J Neurobiol. 40(3):302–315. doi:10.1002/(SICI)1097-4695(19990905)40:3<302::AID-NEU3>3.0.CO;2-7.

Kormos CE, Wilkinson AJ, Davey CJ, Cunningham AJ. 2014. Low birth weight and intelligence in adolescence and early adulthood: a meta-analysis. J Public Health. 36(2):213–224. doi:10.1093/pubmed/fdt071.

Koskenvuo M, Hublin C, Partinen M, Heikkilä K, Kaprio J. 2007. Heritability of diurnal type: a nationwide study of 8753 adult twin pairs. J Sleep Res. 16(2):156–162.

Koskinen S, Lundqvist A, Ristiluoma N. 2012. Terveys, toimintakyky ja hyvinvointi Suomessa 2011. Finland: THL. [accessed 2018 Jan 2]. http://www.julkari.fi/handle/10024/90832.

Koupil I, Leon DA, Lithell HO. 2005. Length of gestation is associated with mortality from cerebrovascular disease. J Epidemiol Community Health. 59(6):473–474. doi:10.1136/jech.2004.026518.

Krause AJ, Simon EB, Mander BA, Greer SM, Saletin JM, Goldstein-Piekarski AN, Walker MP. 2017. The sleep-deprived human brain. Nat Rev Neurosci. 18(7):404–418. doi:10.1038/nrn.2017.55.

Laermans J, Depoortere I. 2016. Chronobesity: role of the circadian system in the obesity epidemic. Obes Rev. 17(2):108–125. doi:10.1111/obr.12351.

Lakens D. 2014. Observed power, and what to do if your editor asks for post-hoc power analyses. [accessed 2018 Jan 2]. http://daniellakens.blogspot.com/2014/12/observed-power-and-what-to-do-if-your.html.

Lampert H. 1939. Reaktionstypenlehre. Dtsch Zahn- Mund- U Kieferheilk. 6:745–750.

Lane JM, Vlasac I, Anderson SG, Kyle SD, Dixon WG, Bechtold DA, Gill S, Little MA, Luik A, Loudon A, et al. 2016. Genome-wide association analysis identifies novel loci for chronotype in 100,420 individuals from the UK Biobank. Nat Commun. 7:10889. doi:10.1038/ncomms10889.

Lawlor DA, Davey Smith G, Clark H, Leon DA. 2006. The associations of birthweight, gestational age and childhood BMI with type 2 diabetes: findings from the Aberdeen Children of the 1950s cohort. Diabetologia. 49(11):2614–2617. doi:10.1007/s00125-006-0408-z.

Lawlor DA, Ebrahim S, Smith GD. 2005. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. Thorax. 60(10):851–858. doi:10.1136/thx.2005.042408.

Lea AJ, Tung J, Archie EA, Alberts SC. 2017. Developmental plasticity - Bridging research in evolution and human health. Evol Med Public Health. 2017(1):162–175. doi:10.1093/emph/eox019.

Lee A, Myung S-K, Cho JJ, Jung Y-J, Yoon JL, Kim MY. 2017. Night Shift Work and Risk of Depression: Meta-analysis of Observational Studies. J Korean Med Sci. 32(7):1091–1096. doi:10.3346/jkms.2017.32.7.1091.

Lenth RV. 2001. Some practical guidelines for effective sample size determination. Am Stat. 55(3):187–193.

Leproult R, Holmbäck U, Cauter EV. 2014. Circadian Misalignment Augments Markers of Insulin Resistance and Inflammation, Independently of Sleep Loss. Diabetes. 63(6):1860–1869. doi:10.2337/db13-1546.

Levandovski R, Sasso E, Hidalgo MP. 2013. Chronotype: a review of the advances, limits and applicability of the main instruments used in the literature to assess human phenotype. Trends Psychiatry Psychother. 35(1):3–11.

Lipnevich AA, Credè M, Hahn E, Spinath FM, Roberts RD, Preckel F. 2017. How distinctive are morningness and eveningness from the Big Five factors of personality? A meta-analytic investigation. J Pers Soc Psychol. 112(3):491–509. doi:10.1037/pspp0000099.

Littner M, Kushida CA, Anderson WM, Bailey D, Berry RB, Davila DG, Hirshkowitz M, Kapen S, Kramer M, Loube D. 2003. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep. 26(3):337–341.

Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, Lawn JE, Cousens S, Mathers C, Black RE. 2016. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. The Lancet. 388(10063):3027–3035.

Liu T-Z, Xu C, Rota M, Cai H, Zhang C, Shi M-J, Yuan R-X, Weng H, Meng X-Y, Kwong JSW, et al. 2017. Sleep duration and risk of all-cause mortality: A flexible, non-linear, meta-regression of 40 prospective cohort studies. Sleep Med Rev. 32:28–36. doi:10.1016/j.smrv.2016.02.005.

Lodemore MR, Petersen SA, Wailoo MP. 1992. Factors affecting the development of night time temperature rhythms. Arch Dis Child. 67(10):1259–1261. doi:10.1136/adc.67.10.1259.

Loomis AL, Harvey EN, Hobart G. 1935. Potential Rhythms of the Cerebral Cortex During Sleep. Science. 81(2111):597–598. doi:10.1126/science.81.2111.597.

Lorenz JM, Wooliever DE, Jetton JR, Paneth N. 1998. A Quantitative Review of Mortality and Developmental Disability in Extremely Premature Newborns. Arch Pediatr Adolesc Med. 152(5):425–435. doi:10.1001/archpedi.152.5.425.

Lund LK, Vik T, Lydersen S, Løhaugen GC, Skranes J, Brubakk A-M, Indredavik MS. 2012. Mental health, quality of life and social relations in young adults born with low birth weight. Health Qual Life Outcomes. 10(1):146.

van Lunenburg A, van der Pal SM, van Dommelen P, van der Pal–de KM, Gravenhorst JB, Verrips GH. 2013. Changes in quality of life into adulthood after very preterm birth and/or very low birth weight in the Netherlands. Health Qual Life Outcomes. 11(1):51.

Magnusson K. 2014. Interpreting Cohen's d effect size. R Psychol. [accessed 2019 Jan 11]. http://rpsychologist.com/d3/cohend/.

de Mairan J-J d'Ortoun. 1729. Observation botanique. Hist Acad Roy Sci.:35–6.

March of Dimes, PMNCH, Save the children, WHO. 2012. Born too soon: the global action report on preterm birth. Howson C, Kinney M, Lawn JE, editors. Geneva: World Health Organization. [accessed 2017 Dec 29]. http://www.who.int/pmnch/media/news/2012/201204%5Fborntoosoon-report.pdf.

Martin SK, Eastman CI. 2002. Sleep Logs of Young Adults with Self-Selected Sleep Times Predict the Dim Light Melatonin Onset. Chronobiol Int. 19(4):695–707. doi:10.1081/CBI-120006080.

Marx R, Tanner-Smith EE, Davison CM, Ufholz L-A, Freeman J, Shankar R, Newton L, Brown RS, Parpia AS, Cozma I, et al. 2017. Later school start times for supporting the education, health, and well-being of high school students. Cochrane Database Syst Rev.(7). doi:10.1002/14651858.CD009467.pub2.

Mathewson KJ, Chow CHT, Dobson KG, Pope EI, Schmidt LA, Van Lieshout RJ. 2017. Mental health of extremely low birth weight survivors: A systematic review and meta-analysis. Psychol Bull. 143(4):347–383. doi:10.1037/bul0000091.

Matricciani L, Bin YS, Lallukka T, Kronholm E, Dumuid D, Paquet C, Olds T. 2017. Past, present, and future: trends in sleep duration and implications for public health. Sleep Health. 3(5):317–323. doi:10.1016/j.sleh.2017.07.006.

Matthews KA, Patel SR, Pantesco EJ, Buysse DJ, Kamarck TW, Lee L, Hall MH. 2018. Similarities and differences in estimates of sleep duration by polysomnography, actigraphy, diary, and self-reported habitual sleep in a community sample. Sleep Health. 4(1):96–103. doi:10.1016/j.sleh.2017.10.011.

Maurer N, Perkinson-Gloor N, Stalder T, Hagmann-von Arx P, Brand S, Holsboer-Trachsler E, Wellmann S, Grob A, Weber P, Lemola S. 2016. Salivary and hair glucocorticoids and sleep in very preterm children during school age. Psychoneuroendocrinology. 72:166–174. doi:10.1016/j.psyneuen.2016.07.003.

McGraw K, Hoffmann R, Harker C, Herman JH. 1999. The development of circadian rhythms in a human infant. Sleep. 22(3):303–310.

McGraw KO, Wong SP. 1992. A common language effect size statistic. Psychol Bull. 111(2):361–365.

McMillen IC, Kok JSM, Adamson TM, Deayton JM, Nowak R. 1991. Development of Circadian Sleep-Wake Rhythms in Preterm and Full-Term Infants. Pediatr Res. 29(4):381–384. doi:10.1203/00006450-199104000-00010.

van Melick MJGJ, van Beukering MDM, Mol BW, Frings-Dresen MHW, Hulshof CTJ. 2014. Shift work, long working hours and preterm birth: a systematic review and meta-analysis. Int Arch Occup Environ Health. 87(8):835–849. doi:10.1007/s00420-014-0934-9.

Menon R. 2008. Spontaneous preterm birth, a clinical dilemma: Etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta Obstet Gynecol Scand. 87(6):590–600. doi:10.1080/00016340802005126.

Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Vartiainen E, Partonen T. 2015. Circadian preference links to depression in general

adult population. J Affect Disord. 188:143–148. doi:10.1016/j.jad.2015.08.061.

Merikanto I, Lahti J, Kuula L, Heinonen K, Räikkönen K, Andersson S, Strandberg T, Pesonen A-K. 2018. Circadian preference and sleep timing from childhood to adolescence in relation to genetic variants from a genome-wide association study. Sleep Med. 50:36–41. doi:10.1016/j.sleep.2018.04.015.

Merikanto I, Lahti T, Kronholm E, Peltonen M, Laatikainen T, Vartiainen E, Salomaa V, Partonen T. 2013. Evening types are prone to depression. Chronobiol Int. 30(5):719–725. doi:10.3109/07420528.2013.784770.

Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, Vartiainen E, Salomaa V, Kronholm E, Partonen T. 2013. Associations of Chronotype and Sleep With Cardiovascular Diseases and Type 2 Diabetes. Chronobiol Int. 30(4):470–477. doi:10.3109/07420528.2012.741171.

Mignot E. 2008. Why We Sleep: The Temporal Organization of Recovery. PLoS Biol. 6(4). doi:10.1371/journal.pbio.0060106.

Miyazaki S, Liu C-Y, Hayashi Y. 2017. Sleep in vertebrate and invertebrate animals, and insights into the function and evolution of sleep. Neurosci Res. 118:3–12. doi:10.1016/j.neures.2017.04.017.

Mongrain V, Lavoie S, Selmaoui B, Paquet J, Dumont M. 2004. Phase Relationships between Sleep-Wake Cycle and Underlying Circadian Rhythms in Morningness-Eveningness. J Biol Rhythms. 19(3):248–257. doi:10.1177/0748730404264365.

Montagna P, Lugaresi E. 2002. Agrypnia Excitata: a generalized overactivity syndrome and a useful concept in the neurophysiopathology of sleep. Clin Neurophysiol. 113(4):552–560. doi:10.1016/S1388-2457(02)00022-6.

Montaruli A, Galasso L, Carandente F, Vitale JA, Roveda E, Caumo A. 2017. If the Morning-Evening Questionnaire (MEQ) is able to predict the actigraphy-based acrophase, how does its reduced, five-item version (rMEQ) perform? Chronobiol Int. 34(4):443–444. doi:10.1080/07420528.2017.1306708.

Moore RY, Eichler VB. 1972. Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. Brain Res. 42(1):201–206. doi:10.1016/0006-8993(72)90054-6.

Morag I, Ohlsson A. 2016. Cycled light in the intensive care unit for preterm and low birth weight infants. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd. [accessed 2017 Dec 29]. http://doi.wiley.com/10.1002/14651858.CD006982.pub4.

Morrison KM, Ramsingh L, Gunn E, Streiner D, Van Lieshout R, Boyle M, Gerstein H, Schmidt L, Saigal S. 2016. Cardiometabolic Health in Adults Born Premature With Extremely Low Birth Weight. Pediatrics. 138(4):e20160515–e20160515. doi:10.1542/peds.2016-0515.

Näsänen-Gilmore P, Sipola-Leppänen M, Tikanmäki M, Matinolli H-M, Eriksson JG, Järvelin M-R, Vääräsmäki M, Hovi P, Kajantie E. 2018. Lung function in adults born preterm. PLOS ONE. 13(10):e0205979. doi:10.1371/journal.pone.0205979.

Natale V, Sansavini A, Trombini E, Esposito MJ, Alessandroni R, Faldella G. 2005. Relationship between preterm birth and circadian typology in adolescence. Neurosci Lett. 382(1–2):139–142. doi:10.1016/j.neulet.2005.03.004.

Natalucci G, Becker J, Becher K, Bickle G, Landolt M, Bucher H. 2013. Self-perceived health status and mental health outcomes in young adults born with less than 1000 g. Acta Paediatr. 102(3):294–299. doi:10.1111/apa.12102.

Nobel Foundation. 2017. The Nobel Prize in Physiology or Medicine 2017. NobelPrize.org. [accessed 2019 Sep 23]. https://www.nobelprize.org/prizes/medicine/2017/press-release/.

Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, MacCabe J, Rifkin L, Hultman CM. 2012. Preterm Birth and Psychiatric Disorders in Young Adult Life. Arch Gen Psychiatry. 69(6). doi:10.1001/archgenpsychiatry.2011.1374.

Onishi S, Miyazawa G, Nishimura Y, Sugiyama S, Yamakawa T, Inagaki H, Katoh T, Itoh S, Isobe K. 1983. Postnatal development of circadian rhythm in serum cortisol levels in children. Pediatrics. 72(3):399–404.

Orozco-Solís R, Matos RJB, Lopes de Souza S, Grit I, Kaeffer B, Manhães de Castro R, Bolaños-Jiménez F. 2011. Perinatal nutrient restriction induces long-lasting alterations in the circadian expression pattern of genes regulating food intake and energy metabolism. Int J Obes. 35(7):990–1000. doi:10.1038/ijo.2010.223.

Oskoui M, Coutinho F, Dykeman J, Jetté N, Pringsheim T. 2013. An update on the prevalence of cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 55(6):509–519. doi:10.1111/dmcn.12080.

Paavonen EJ, Strang-Karlsson S, Räikkonen K, Heinonen K, Pesonen A-K, Hovi P, Andersson S, Järvenpää A-L, Eriksson JG, Kajantie E. 2007. Very Low Birth Weight Increases Risk for Sleep-Disordered Breathing in Young Adulthood: The Helsinki Study of Very Low Birth Weight Adults. Pediatrics. 120(4):778–784. doi:10.1542/peds.2007-0540.

Paine S-J, Gander PH. 2016. Differences in circadian phase and weekday/weekend sleep patterns in a sample of middle-aged morning types and evening types. Chronobiol Int. 33(8):1009–1017. doi:10.1080/07420528.2016.1192187.

Parkinson JRC, Hyde MJ, Gale C, Santhakumaran S, Modi N. 2013. Preterm Birth and the Metabolic Syndrome in Adult Life: A Systematic Review and Meta-analysis. Pediatrics. 131(4):e1240–e1263. doi:10.1542/peds.2012-2177.

Partinen M, Kaprio J, Koskenvuo M, Putkonen P, Langinvainio H. 1983. Genetic and Environmental Determination of Human Sleep. Sleep. 6(3):179–185. doi:10.1093/sleep/6.3.179.

Patterson F, Malone SK, Lozano A, Grandner MA, Hanlon AL. 2016. Smoking, Screen-Based Sedentary Behavior, and Diet Associated with Habitual Sleep Duration and Chronotype: Data from the UK Biobank. Ann Behav Med Publ Soc Behav Med. 50(5):715–726. doi:10.1007/s12160-016-9797-5.

Pellegrino R, Kavakli IH, Goel N, Cardinale CJ, Dinges DF, Kuna ST, Maislin G, Van Dongen HPA, Tufik S, Hogenesch JB, et al. 2014. A Novel BHLHE41 Variant is Associated with Short Sleep and Resistance to Sleep Deprivation in Humans. Sleep. 37(8):1327–1336. doi:10.5665/sleep.3924.

Perkinson-Gloor N, Hagmann-von Arx P, Brand S, Holsboer-Trachsler E, Grob A, Weber P, Lemola S. 2015. The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood. J Psychiatr Res. 60:141–147. doi:10.1016/j.jpsychires.2014.10.005.

Pesonen A-K, Räikkönen K, Heinonen K, Andersson S, Hovi P, Järvenpää A-L, Eriksson JG, Kajantie E. 2008. Personality of young adults born prematurely: the Helsinki study of very low birth weight adults. J Child Psychol Psychiatry. 49(6):609–617. doi:10.1111/j.1469-7610.2007.01874.x.

Petersen SA, Anderson ES, Lodemore M, Rawson D, Wailoo MP. 1991. Sleeping position and rectal temperature. Arch Dis Child. 66(8):976–979. doi:10.1136/adc.66.8.976.

Phillips JB, Abbot P, Rokas A. 2015. Is preterm birth a human-specific syndrome? Evol Med Public Health. 2015(1):136. doi:10.1093/emph/eov010.

Pihkala J, Hakala T, Voutilainen P, Raivio K. 1989. [Characteristic of recent fetal growth curves in Finland]. Duodecim Lääketieteellinen Aikakauskirja. 105(18):1540–1546.

Plikus MV, Vollmers C, Cruz D de la, Chaix A, Ramos R, Panda S, Chuong C-M. 2013. Local circadian clock gates cell cycle progression of transient amplifying cells during regenerative hair cycling. Proc Natl Acad Sci. 110(23):E2106–E2115. doi:10.1073/pnas.1215935110.

Porter TF, Fraser AM, Hunter CY, Ward RH, Varner MW. 1997. The Risk of Preterm Birth Across Generations. Obstet Gynecol. 90(1):63–67.

Post M. 2014. Definitions of Quality of Life: What Has Happened and How to Move On. Top Spinal Cord Inj Rehabil. 20(3):167–180. doi:10.1310/sci2003-167.

Putilov AA. 2017. Owls, larks, swifts, woodcocks and they are not alone: A historical review of methodology for multidimensional self-assessment of individual differences in sleep-wake pattern. Chronobiol Int. 34(3):426–437. doi:10.1080/07420528.2017.1278704.

Pyhälä, Lahti J, Heinonen K, Pesonen A-K, Strang-Karlsson S, Hovi P, Järvenpää A-L, Eriksson JG, Andersson S, Kajantie E. 2011. Neurocognitive abilities in young adults with very low birth weight. Neurology. 77(23):2052–2060.

Pyhälä R, Räikkönen K, Feldt K, Andersson S, Hovi P, Eriksson JG, Järvenpää A-L, Kajantie E. 2009. Blood Pressure Responses to Psychosocial Stress in Young Adults With Very Low Birth Weight: Helsinki Study of Very Low Birth Weight Adults. Pediatrics. 123(2):731–734. doi:10.1542/peds.2008-0277.

Pyhälä R, Räikkönen K, Pesonen A-K, Heinonen K, Lahti J, Hovi P, Strang-Karlsson S, Andersson S, Eriksson JG, Järvenpää A-L, et al. 2011. Parental Bonding after Preterm Birth: Child and Parent Perspectives in the Helsinki Study of Very Low Birth Weight Adults. J Pediatr. 158(2):251-256.e1. doi:10.1016/j.jpeds.2010.07.059.

Pyhälä R, Wolford E, Kautiainen H, Andersson S, Bartmann P, Baumann N, Brubakk A-M, Evensen KAI, Hovi P, Kajantie E. 2017. Self-reported mental health problems among adults born preterm. Pediatrics.

Qiu P, Jiang J, Liu Z, Cai Y, Huang T, Wang Y, Liu Q, Nie Y, Liu F, Cheng J, et al. 2019. BMAL1 knockout macaque monkeys display reduced sleep and psychiatric disorders. Natl Sci Rev. doi:10.1093/nsr/nwz002.

Raju TNK, Higgins RD, Stark AR, Leveno KJ. 2006. Optimizing Care and Outcome for Late-Preterm (Near-Term) Infants: A Summary of the Workshop Sponsored by the National Institute of Child Health and Human Development. Pediatrics. 118(3):1207–1214. doi:10.1542/peds.2006-0018.

Randler C, Bilger S, Díaz-Morales JF. 2009. Associations among Sleep, Chronotype, Parental Monitoring, and Pubertal Development among German Adolescents. J Psychol Prov. 143(5):509–20.

Randler C, Faßl C, Kalb N. 2017. From Lark to Owl: developmental changes in morningness-eveningness from new-borns to early adulthood. Sci Rep. 7(1). doi:10.1038/srep45874.

Rechtschaffen A, Bergmann BM. 2002. Sleep Deprivation in the Rat: An Update of the 1989 Paper. Sleep. 25(1):18–24. doi:10.1093/sleep/25.1.18.

Reppert SM, Weaver DR. 2002. Coordination of circadian timing in mammals. Nature. 418(6901):935–941. doi:10.1038/nature00965.

Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL, Cauter EV. 2013. Chronotype Is Independently Associated With

Glycemic Control in Type 2 Diabetes. Diabetes Care. 36(9):2523–2529. doi:10.2337/dc12-2697.

Richards J, Gumz ML. 2012. Advances in understanding the peripheral circadian clocks. FASEB J. 26(9):3602–3613. doi:10.1096/fj.12-203554.

Rivkees SA. 2004. Emergence and influences of circadian rhythmicity in infants. Clin Perinatol. 31(2):217–228. doi:10.1016/j.clp.2004.04.011.

Rivkees SA, Mayes L, Jacobs H, Gross I. 2004. Rest-Activity Patterns of Premature Infants Are Regulated by Cycled Lighting. Pediatrics. 113(4):833–839. doi:10.1542/peds.113.4.833.

Roenneberg T. 2012. Five myths about sleep. Wash Post. [accessed 2019 Feb 4]. www.washingtonpost.com/opinions/five-myths-about-sleep/2012/11/21/4e1c9f44-3273-11e2-bb9b-288a310849ee_story.html.

Roenneberg T, Daan S, Merrow M. 2003. The Art of Entrainment. J Biol Rhythms. 18(3):183–194. doi:10.1177/0748730403018003001.

Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, Merrow M. 2007. Epidemiology of the human circadian clock. Sleep Med Rev. 11(6):429–438. doi:10.1016/j.smrv.2007.07.005.

Roenneberg T, Kuehnle T, Pramstaller PP, Ricken J, Havel M, Guth A, Merrow M. 2004. A marker for the end of adolescence. Curr Biol. 14(24):R1038–R1039. doi:10.1016/j.cub.2004.11.039.

Roenneberg T, Merrow M. 2007. Entrainment of the Human Circadian Clock. Cold Spring Harb Symp Quant Biol. 72(1):293–299. doi:10.1101/sqb.2007.72.043.

Roenneberg T, Wirz-Justice A, Merrow M. 2003. Life between Clocks: Daily Temporal Patterns of Human Chronotypes. J Biol Rhythms. 18(1):80–90. doi:10.1177/0748730402239679.

Ross JJ. 1965. Neurological Findings After Prolonged Sleep Deprivation. Arch Neurol. 12(4):399–403. doi:10.1001/archneur.1965.00460280069006.

Rowe M, McCrae C, Campbell J, Horne C, Tiegs T, Lehman B, Cheng J. 2008. Actigraphy in Older Adults: Comparison of Means and Variability of Three Different Aggregates of Measurement. Behav Sleep Med. 6(2):127–145. doi:10.1080/15402000801952872.

Rumble ME, Dickson D, McCall WV, Krystal AD, Case D, Rosenquist PB, Benca RM. 2018. The relationship of person-specific eveningness chronotype, greater seasonality, and less rhythmicity to suicidal behavior: A literature review. J Affect Disord. 227:721–730. doi:10.1016/j.jad.2017.11.078.

Ruscio J. 2008. A probability-based measure of effect size: Robustness to base rates and other factors. Psychol Methods. 13(1):19–30. doi:10.1037/1082-989X.13.1.19.

Saad NJ, Patel J, Burney P, Minelli C. 2017. Birth Weight and Lung Function in Adulthood: A Systematic Review and Meta-analysis. Ann Am Thorac Soc. 14(6):994–1004. doi:10.1513/AnnalsATS.201609-746SR.

Saigal S. 2014. Preemie Voices. Young men and women born very prematurely describe their lives, challenges and achievements. FriesenPress.

Saigal S, Ferro MA, Van Lieshout RJ, Schmidt LA, Morrison KM, Boyle MH. 2016. Health-Related Quality of Life Trajectories of Extremely Low Birth Weight Survivors into Adulthood. J Pediatr. 179:68-73.e1. doi:10.1016/j.jpeds.2016.08.018.

Saigal S, Stoskopf B, Boyle M, Paneth N, Pinelli J, Streiner D, Goddeeris J. 2007. Comparison of Current Health, Functional Limitations, and Health Care Use of Young Adults Who Were Born With Extremely Low Birth Weight and Normal Birth Weight. Pediatrics. 119(3):e562–e573. doi:10.1542/peds.2006-2328.

Saigal S, Stoskopf B, Pinelli J, Streiner D, Hoult L, Paneth N, Goddeeris J. 2006. Self-Perceived Health-Related Quality of Life of Former Extremely Low Birth Weight Infants at Young Adulthood. Pediatrics. 118(3):1140–1148. doi:10.1542/peds.2006-0119.

Salonen MK, Wasenius N, Kajantie E, Lano A, Lahti J, Heinonen K, Räikkönen K, Eriksson JG. 2015. Physical Activity, Body Composition and Metabolic Syndrome in Young Adults. PLOS ONE. 10(5):e0126737. doi:10.1371/journal.pone.0126737.

Santisteban JA, Brown TG, Gruber R. 2018. Association between the Munich Chronotype Questionnaire and Wrist Actigraphy. Sleep Disord. doi:10.1155/2018/5646848.

Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. 2014. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2(6):e323–e333. doi:10.1016/S2214-109X(14)70227-X.

von Schantz M. 2017. Chapter Three - Natural Variation in Human Clocks. In: Goodwin SF, editor. Advances in Genetics. Vol. 99. Academic Press. (Natural Variation and Clocks). p. 73–96.

von Schantz M, Taporoski TP, Horimoto ARVR, Duarte NE, Vallada H, Krieger JE, Pedrazzoli M, Negrão AB, Pereira AC. 2015. Distribution and heritability of diurnal preference (chronotype) in a rural Brazilian family-based cohort, the Baependi study. Sci Rep. 5:9214. doi:10.1038/srep09214.

Scheer FAJL, Hilton MF, Mantzoros CS, Shea SA. 2009. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci. 106(11):4453–4458. doi:10.1073/pnas.0808180106.

Scheer FAJL, Jr KPW, Kronauer RE, Czeisler CA. 2007. Plasticity of the Intrinsic Period

of the Human Circadian Timing System. PLOS ONE. 2(8):e721. doi:10.1371/journal.pone.0000721.

Schuch JB, Genro JP, Bastos CR, Ghisleni G, Tovo-Rodrigues L. 2018. The role of CLOCK gene in psychiatric disorders: Evidence from human and animal research. Am J Med Genet B Neuropsychiatr Genet. 177(2):181–198. doi:10.1002/ajmg.b.32599.

Schwartz MD, Kilduff TS. 2015. The neurobiology of sleep and wakefulness. Psychiatr Clin North Am. 38(4):615–644. doi:10.1016/j.psc.2015.07.002.

Sei H, Sakata-Haga H, Ohta K, Sawada K, Morita Y, Fukui Y. 2003. Prenatal exposure to alcohol alters the light response in postnatal circadian rhythm. Brain Res. 987(1):131–134.

Seidner G, Robinson JE, Wu M, Worden K, Masek P, Roberts SW, Keene AC, Joiner WJ. 2015. Identification of neurons with a privileged role in sleep homeostasis in Drosophila melanogaster. Curr Biol CB. 25(22):2928–2938. doi:10.1016/j.cub.2015.10.006.

Sellier E, Platt MJ, Andersen GL, Krägeloh-Mann I, De La Cruz J, Cans C, Surveillance of Cerebral Palsy Network. 2016. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. Dev Med Child Neurol. 58(1):85–92. doi:10.1111/dmcn.12865.

Serón-Ferré M, Mendez N, Abarzua-Catalan L, Vilches N, Valenzuela FJ, Reynolds HE, Llanos AJ, Rojas A, Valenzuela GJ, Torres-Farfan C. 2012. Circadian rhythms in the fetus. Mol Cell Endocrinol. 349(1):68–75. doi:10.1016/j.mce.2011.07.039.

Shachar B, Mayo J, Lyell D, Baer R, Jeliffe-Pawlowski L, Stevenson D, Shaw G. 2016. Interpregnancy interval after live birth or pregnancy termination and estimated risk of preterm birth: a retrospective cohort study. BJOG Int J Obstet Gynaecol. 123(12):2009–2017. doi:10.1111/1471-0528.14165.

Shaw GM, Wise PH, Mayo J, Carmichael SL, Ley C, Lyell DJ, Shachar BZ, Melsop K, Phibbs CS, Stevenson DK, et al. 2014. Maternal Prepregnancy Body Mass Index and Risk of Spontaneous Preterm Birth: BMI and preterm birth risk. Paediatr Perinat Epidemiol. 28(4):302–311. doi:10.1111/ppe.12125.

Shaw PJ, Tononi G, Greenspan RJ, Robinson DF. 2002. Stress response genes protect against lethal effects of sleep deprivation in *Drosophila*. Nature. 417(6886):287–291. doi:10.1038/417287a.

Sheehan CM, Frochen SE, Walsemann KM, Ailshire JA. 2018. Are U.S. adults reporting less sleep?: Findings from sleep duration trends in the National Health Interview Survey, 2004–2017. Sleep. 42(2):1–8. doi:10.1093/sleep/zsy221.

Sheikh IA, Ahmad E, Jamal MS, Rehan M, Assidi M, Tayubi IA, AlBasri SF, Bajouh OS, Turki RF, Abuzenadah AM, et al. 2016. Spontaneous preterm birth and single nucleotide gene polymorphisms: a recent update. BMC Genomics. 17(9):759. doi:10.1186/s12864-016-3089-0.

Shimada M, Takahashi K, Segawa M, Higurashi M, Samejim M, Horiuchi K. 1999. Emerging and entraining patterns of the sleep–wake rhythm in preterm and term infants. Brain Dev. 21(7):468–473. doi:10.1016/S0387-7604(99)00054-6.

Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Hovi P, Miettola S, Ruokonen A, Pouta A, Järvelin M-R, Kajantie E. 2014. Cardiovascular Risk Factors in Adolescents Born Preterm. Pediatrics. 134(4):e1072–e1081. doi:10.1542/peds.2013-4186.

Smith CS, Reilly C, Midkiff K. 1989. Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. J Appl Psychol. 74(5):728–738. doi:10.1037/0021-9010.74.5.728.

Smith L, Canal MM. 2009. Expression of Circadian Neuropeptides in the Hypothalamus of Adult Mice is Affected by Postnatal Light Experience. J Neuroendocrinol. 21(11):946–953. doi:10.1111/j.1365-2826.2009.01914.x.

Smith LK, Draper ES, Manktelow BN, Dorling JS, Field DJ. 2007. Socioeconomic inequalities in very preterm birth rates. Arch Dis Child - Fetal Neonatal Ed. 92(1):F11–F14. doi:10.1136/adc.2005.090308.

Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, Carden KA. 2018. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med. 14(7):1209–1230. doi:10.5664/jcsm.7228.

Someren EJWV. 2007. Improving actigraphic sleep estimates in insomnia and dementia: how many nights? J Sleep Res. 16(3):269–275. doi:10.1111/j.1365-2869.2007.00592.x.

Stangenes KM, Fevang SK, Grundt J, Donkor HM, Markestad T, Hysing M, Elgen IB, Bjorvatn B. 2017. Children born extremely preterm had different sleeping habits at 11 years of age and more childhood sleep problems than term-born children. Acta Paediatr. 106(12):1966–1972. doi:10.1111/apa.13991.

Stanley N. Napoleon and sleep. [accessed 2019 Feb 4]. http://www.thesleepconsultancy.com/napoleon.htm.

Stephan FK, Zucker I. 1972. Circadian Rhythms in Drinking Behavior and Locomotor Activity of Rats Are Eliminated by Hypothalamic Lesions. Proc Natl Acad Sci U S A. 69(6):1583–1586.

Stephenson R, Chu KM, Lee J. 2007. Prolonged deprivation of sleep-like rest raises metabolic rate in the Pacific beetle cockroach,

Diploptera punctata (Eschscholtz). J Exp Biol. 210(14):2540–2547. doi:10.1242/jeb.005322.

Strang-Karlsson S, Kajantie E, Pesonen A-K, Räikkönen K, Hovi P, Lahti J, Heinonen K, Järvenpää A-L, Eriksson JG, Andersson S, et al. 2010. Morningness propensity in young adults born prematurely: The Helsinki Study of Very Low Birth Weight Adults. Chronobiol Int. 27(9–10):1829–1842. doi:10.3109/07420528.2010.512689.

Strang-Karlsson S, Räikkonen K, Kajantie E, Andersson S, Hovi P, Heinonen K, Pesonen A-K, Järvenpää A-L, Eriksson JG, Paavonen EJ. 2007. Sleep Quality in Young Adults with Very Low Birth Weight--the Helsinki Study of Very Low Birth Weight Adults. J Pediatr Psychol. 33(4):387–395. doi:10.1093/jpepsy/jsm125.

Suh S, Yang H-C, Kim N, Yu JH, Choi S, Yun C-H, Shin C. 2017. Chronotype Differences in Health Behaviors and Health-Related Quality of Life: A Population-Based Study Among Aged and Older Adults. Behav Sleep Med. 15(5):361–376. doi:10.1080/15402002.2016.1141768.

Sumová A, Bendová Z, Sládek M, El-Hennamy R, Laurinová K, Jindráková Z, Illnerová H. 2006. Setting the biological time in central and peripheral clocks during ontogenesis. FEBS Lett. 580(12):2836–2842. doi:10.1016/j.febslet.2006.03.023.

Sumová A, Čečmanová V. 2018. Mystery of rhythmic signal emergence within the suprachiasmatic nuclei. Eur J Neurosci. doi:10.1111/ejn.14141.

Sun M, Feng W, Wang F, Li P, Li Z, Li M, Tse G, Vlaanderen J, Vermeulen R, Tse LA. 2018. Meta-analysis on shift work and risks of specific obesity types. Obes Rev. 19(1):28–40. doi:10.1111/obr.12621.

Sutton GM, Centanni AV, Butler AA. 2010. Protein Malnutrition during Pregnancy in C57BL/6J Mice Results in Offspring with Altered Circadian Physiology before Obesity. Endocrinology. 151(4):1570–1580. doi:10.1210/en.2009-1133.

Tahara Y, Aoyama S, Shibata S. 2017. The mammalian circadian clock and its entrainment by stress and exercise. J Physiol Sci. 67(1):1–10. doi:10.1007/s12576-016-0450-7.

Tahara Y, Shibata S. 2018. Entrainment of the mouse circadian clock: Effects of stress, exercise, and nutrition. Free Radic Biol Med. 119:129–138. doi:10.1016/j.freeradbiomed.2017.12.026.

Tähkämö L, Partonen T, Pesonen A-K. 2018. Systematic review of light exposure impact on human circadian rhythm. Chronobiol Int. 36(2):151-170. doi:10.1080/07420528.2018.1527773.

Takeda N, Maemura K. 2015. The role of clock genes and circadian rhythm in the development of cardiovascular diseases. Cell Mol Life Sci. 72(17):3225–3234. doi:10.1007/s00018-015-1923-1.

Taylor BJ, Hasler BP. 2018. Chronotype and Mental Health: Recent Advances. Curr Psychiatry Rep. 20(8):59. doi:10.1007/s11920-018-0925-8.

The Merriam Webster Dictionary. Circadian | Definition of Circadian by Merriam-Webster. [accessed 2019 Sep 20]. https://www.merriam-webster.com/dictionary/circadian.

Thomson W. 1889. Popular lectures and addresses. London and New York: Macmillan and co (Nature Series). [accessed 2019 Sep 17]. https://archive.org/stream/popularlecturesa01kelvuoft#page/n7/mode/2up.

Tideman E, Ley D, Bjerre I, Forslund M. 2001. Longitudinal follow-up of children born preterm: somatic and mental health, self-esteem and quality of life at age 19. Early Hum Dev. 61(2):97–110.

Tikanmäki M, Kaseva N, Tammelin T, Sipola-Leppänen M, Matinolli H-M, Eriksson JG, Järvelin M-R, Vääräsmäki M, Kajantie E. 2017. Leisure Time Physical Activity in Young Adults Born Preterm. J Pediatr. 189:135-142.e2. doi:10.1016/j.jpeds.2017.06.068.

Tikanmäki M, Tammelin T, Kaseva N, Sipola-Leppänen M, Matinolli H-M, Hakonen H, Ekelund U, Eriksson JG, Järvelin M-R, Vääräsmäki M, et al. 2017. Objectively measured physical activity and sedentary time in young adults born preterm—The ESTER study. Pediatr Res. 81(4):550–555. doi:10.1038/pr.2016.262.

Tikanmäki M, Tammelin T, Sipola-Leppänen M, Kaseva N, Matinolli H-M, Miettola S, Eriksson JG, Järvelin M-R, Vääräsmäki M, Kajantie E. 2016. Physical Fitness in Young Adults Born Preterm. Pediatrics. 137(1):e20151289. doi:10.1542/peds.2015-1289.

Tonetti L, Fabbri M, Natale V. 2009. Relationship between Circadian Typology and Big Five Personality Domains. Chronobiol Int. 26(2):337–347. doi:10.1080/07420520902750995.

Tonetti L, Natale V, Randler C. 2015. Association between circadian preference and academic achievement: A systematic review and meta-analysis. Chronobiol Int. 32(6):792–801. doi:10.3109/07420528.2015.1049271.

Tononi G, Cirelli C. 2014. Sleep and the Price of Plasticity: From Synaptic and Cellular Homeostasis to Memory Consolidation and Integration. Neuron. 81(1):12–34. doi:10.1016/j.neuron.2013.12.025.

Torrance GW. 1987. Utility approach to measuring health-related quality of life. J Chronic Dis. 40(6):593–603.

Tryon WW. 2004. Issues of validity in actigraphic sleep assessment. Sleep. 27(1):158–165.

Ueda P, Cnattingius S, Stephansson O, Ingelsson E, Ludvigsson JF, Bonamy A-KE. 2014. Cerebrovascular and ischemic heart disease in young adults born preterm: a population-based Swedish cohort study. Eur J Epidemiol. 29(4):253–260. doi:10.1007/s10654-014-9892-5.

Ulrich M, Mortensen EL, Jensen C, Kamper J. 2013. On the well-being of adult expremies in Denmark. Acta Paediatr. 102(6):602–606. doi:10.1111/apa.12196.

Van De Water ATM, Holmes A, Hurley DA. 2011. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography – a systematic review. J Sleep Res. 20(1pt2):183–200. doi:10.1111/j.1365-2869.2009.00814.x.

Vederhus BJ, Eide GE, Natvig GK, Markestad T, Graue M, Halvorsen T. 2015. Health-related quality of life and emotional and behavioral difficulties after extreme preterm birth: developmental trajectories. PeerJ. 3:e738. doi:10.7717/peerj.738.

Verrips G, Brouwer L, Vogels T, Taal E, Drossaert C, Feeny D, Verheijden M, Verloove-Vanhorick P. 2012. Long term follow-up of health-related quality of life in young adults born very preterm or with a very low birth weight. Health Qual Life Outcomes. 10(1):49.

Vetter C. 2018. Circadian disruption: What do we actually mean? Eur J Neurosci. 00:1-20. doi:10.1111/ejn.14255.

Vink J. M., Vink Jacqueline M., Groot AS, Kerkhof GA, Boomsma DI. 2001. Genetic Analysis of Morningness and Eveningness. Chronobiol Int. 18(5):809–822. doi:10.1081/CBI-100107516.

Vitale JA, Roveda E, Montaruli A, Galasso L, Weydahl A, Caumo A, Carandente F. 2015. Chronotype influences activity circadian rhythm and sleep: Differences in sleep quality between weekdays and weekend. Chronobiol Int. 32(3):405–415. doi:10.3109/07420528.2014.986273.

Vuori E, Gissler M. 2016. Perinataalitilasto – synnyttäjät, synnytykset ja vastasyntyneet 2015. Perinatalstatistik – föderskor, förlossningar och nyfödda 2015. [accessed 2018 Jan 2]. http://www.julkari.fi/handle/10024/131259.

Wahlstrom K, Dretzke B, Gordon M, Peterson K, Edwards K, Gdula J. 2014. Examining the Impact of Later School Start Times on the Health and Academic Performance of High School Students: A Multi -Site Study. Center for Applied Resea rch and Educational Improvement. St Paul, MN: University of Minnesota. [accessed 2018 Dec 26]. https://conservancy.umn.edu/bitstream/handle/11299/162769/Impact%20of%20Later%20Start%20Time%20Final%20Report.pdf.

Wang T, Huang T, Li Y, Zheng Y, Manson JE, Hu FB, Qi L. 2016. Low birthweight and risk of type 2 diabetes: a Mendelian randomisation study. Diabetologia. 59(9):1920–1927. doi:10.1007/s00125-016-4019-z.

Warrener AG, Lewton KL, Pontzer H, Lieberman DE. 2015. A Wider Pelvis Does Not Increase Locomotor Cost in Humans, with Implications for the Evolution of Childbirth. PLOS ONE. 10(3):e0118903. doi:10.1371/journal.pone.0118903.

Washburn SL. 1960. Tools and human evolution. Sci Am. 203:63–75.

Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, et al. 2015. Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society on the Recommended Amount of Sleep for a Healthy Adult: Methodology and Discussion. Sleep. 38(8):1161–1183. doi:10.5665/sleep.4886.

Watson NF, Buchwald D, Harden KP. 2013. A twin study of genetic influences on diurnal preference and risk for alcohol use outcomes. J Clin Sleep Med. 9(12):1333–1339. doi:10.5664/jcsm.3282.

Watts AL, Norbury R. 2017. Reduced Effective Emotion Regulation in Night Owls. J Biol Rhythms. 32(4):369–375. doi:10.1177/0748730417709111.

Wells JCK, DeSilva JM, Stock JT. 2012. The obstetric dilemma: An ancient game of Russian roulette, or a variable dilemma sensitive to ecology? Am J Phys Anthropol. 149(S55):40–71. doi:10.1002/ajpa.22160.

Wennman H, Kronholm E, Partonen T, Peltonen M, Vasankari T, Borodulin K. 2015. Evening typology and morning tiredness associates with low leisure time physical activity and high sitting. Chronobiol Int. 32(8):1090–1100. doi:10.3109/07420528.2015.1063061.

WHO. 1947. CONSTITUTION of the World Health Organization. Chron World Health Organ. 1(1–2):29–43.

Wilcox AJ, Skjaerven R, Lie RT. 2008. Familial Patterns of Preterm Delivery: Maternal and Fetal Contributions. Am J Epidemiol. 167(4):474–479. doi:10.1093/aje/kwm319.

Winkvist A, Mogren I, Högberg U. 1998. Familial patterns in birth characteristics: impact on individual and population risks. Int J Epidemiol. 27(2):248–254.

Wirz-Justice A. 2007. How to measure circadian rhythms in humans. Medicographia. 29(1):84–90.

Wittenbrink N, Ananthasubramaniam B, Münch M, Koller B, Maier B, Weschke C, Bes F, Zeeuw J de, Nowozin C, Wahnschaffe A, et al. 2018. High-accuracy determination of internal circadian time from a single blood sample. J Clin Invest. 128(9):3826–3839. doi:10.1172/JCI120874.

Wittman AB, Wall LL. 2007. The Evolutionary Origins of Obstructed Labor: Bipedalism, Encephalization, and the Human Obstetric Dilemma. Obstet Gynecol Surv. 62(11):739–748. doi:10.1097/01.ogx.0000286584.04310.5c.

Wittmann M, Dinich J, Merrow M, Roenneberg T. 2006. Social Jetlag: Misalignment of Biological and Social Time. Chronobiol Int. 23(1–2):497–509. doi:10.1080/07420520500545979.

Wittmann M, Paulus M, Roenneberg T. 2010. Decreased Psychological Well-Being in Late

"Chronotypes" Is Mediated by Smoking and Alcohol Consumption. Subst Use Misuse. 45(1/2):15–30. doi:10.3109/10826080903498952.

Woelfle MA, Ouyang Y, Phanvijhitsiri K, Johnson CH. 2004. The Adaptive Value of Circadian Clocks: An Experimental Assessment in Cyanobacteria. Curr Biol.:6.

Wong PM, Hasler BP, Kamarck TW, Muldoon MF, Manuck SB. 2015. Social Jetlag, Chronotype, and Cardiometabolic Risk. J Clin Endocrinol Metab. 100(12):4612–4620. doi:10.1210/jc.2015-2923.

World Health Organization. 2012. Trends in maternal mortality: 1990 to 2010: WHO, UNICEF, UNFPA and the World Bank estimates. Geneva: World Health Organization.

Wright KP, McHill AW, Birks BR, Griffin BR, Rusterholz T, Chinoy ED. 2013. Entrainment of the Human Circadian Clock to the Natural Light-Dark Cycle. Curr Biol. 23(16):1554–1558. doi:10.1016/j.cub.2013.06.039.

Yagita K. 2001. Molecular Mechanisms of the Biological Clock in Cultured Fibroblasts. Science. 292(5515):278–281. doi:10.1126/science.1059542.

Yan L. 2009. Expression of clock genes in the suprachiasmatic nucleus: Effect of environmental lighting conditions. Rev Endocr Metab Disord. 10(4):301–310. doi:10.1007/s11154-009-9121-9.

Yetish G, Kaplan H, Gurven M, Wood B, Pontzer H, Manger PR, Wilson C, McGregor R, Siegel JM. 2015. Natural Sleep and Its Seasonal Variations in Three Pre-industrial Societies. Curr Biol. 25(21):2862–2868. doi:10.1016/j.cub.2015.09.046.

Yeung SLA, Lin SL, Li AM, Schooling CM. 2016. Birth weight and risk of ischemic heart disease: A Mendelian randomization study. Sci Rep. 6:38420. doi:10.1038/srep38420.

Yiallourou SR, Arena BC, Wallace EM, Odoi A, Hollis S, Weichard A, Horne RS. 2017. Being Born Too Small and Too Early May Alter Sleep in Childhood. Sleep. doi: 10.1093/sleep/zsx193

Yoo S-H, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, Buhr ED, Siepka SM, Hong H-K, Oh WJ, Yoo OJ, et al. 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. Proc Natl Acad Sci. 101(15):5339–5346. doi:10.1073/pnas.0308709101.

Yu JH, Yun C-H, Ahn JH, Suh S, Cho HJ, Lee SK, Yoo HJ, Seo JA, Kim SG, Choi KM, et al. 2015. Evening Chronotype Is Associated With Metabolic Disorders and Body Composition in Middle-Aged Adults. J Clin Endocrinol Metab. 100(4):1494–1502. doi:10.1210/jc.2014-3754.

Zaki NFW, Spence DW, BaHammam AS, Pandi-Perumal SR, Cardinali DP, Brown GM. 2018. Chronobiological theories of mood disorder. Eur Arch Psychiatry Clin Neurosci. 268(2):107–118. doi:10.1007/s00406-017-0835-5.

Zanquetta MM, Corrêa-Giannella ML, Monteiro MB, Villares SM. 2010. Body weight, metabolism and clock genes. Diabetol Metab Syndr. 2(1). doi:10.1186/1758-5996-2-53.

Zavada A, Gordijn MCM, Beersma DGM, Daan S, Roenneberg T. 2005. Comparison of the Munich Chronotype Questionnaire with the Horne-Östberg's Morningness-Eveningness score. Chronobiol Int. 22(2):267–278. doi:10.1081/CBI-200053536.

Zerbini G, Merrow M. 2017. Time to learn: How chronotype impacts education. PsyCh J. 6(4):263–276. doi:10.1002/pchj.178.

Zeve D, Regelmann MO, Holzman IR, Rapaport R. 2016. Small at Birth, but How Small? The Definition of SGA Revisited. Horm Res Paediatr. 86(5):357–360. doi:10.1159/000449275.

Zhai L, Zhang H, Zhang D. 2015. Sleep Duration and Depression Among Adults: A Meta-Analysis of Prospective Studies. Depress Anxiety. 32(9):664–670. doi:10.1002/da.22386.

Zhang G, Feenstra B, Bacelis J, Liu X, Muglia LM, Juodakis J, Miller DE, Litterman N, Jiang P-P, Russell L, et al. 2017. Genetic Associations with Gestational Duration and Spontaneous Preterm Birth. N Engl J Med. 377(12):1156–1167. doi:10.1056/NEJMoa1612665.

Zhang G, Srivastava A, Bacelis J, Juodakis J, Jacobsson B, Muglia LJ. 2018. Genetic studies of gestational duration and preterm birth. Best Pract Res Clin Obstet Gynaecol. 52:33–47. doi:10.1016/j.bpobgyn.2018.05.003.

Zhang L, Fu Y-H. 2018. The molecular genetics of human sleep. Eur J Neurosci. doi:10.1111/ejn.14132.

Zöller B, Sundquist J, Sundquist K, Crump C. 2015. Perinatal risk factors for premature ischaemic heart disease in a Swedish national cohort. BMJ Open. 5(6). doi:10.1136/bmjopen-2014-007308.

Appendix:

Original publications

I **Björkqvist J, Paavonen J, Andersson S, Pesonen A-K, Lahti J, Heinonen K, Eriksson J, Räikkönen K, Hovi P, Kajantie E, Strang-Karlsson S. 2014. Advanced sleep–wake rhythm in adults born prematurely: confirmation by actigraphy-based assessment in the Helsinki Study of Very Low Birth Weight Adults. Sleep Med. 15:1101–1106.**

"… as the author of this Elsevier article, you retain the right to include it in a thesis or dissertation, provided it is not published commercially. Permission is not required, but please ensure that you reference the journal as the original source."

II **Björkqvist J, Kuula J, Kuula L, Nurhonen M, Räikkönen R, Hovi P, Pesonen A, Kajantie E. "Chronotype in very low birth weight adults – a sibling study" (submitted).**

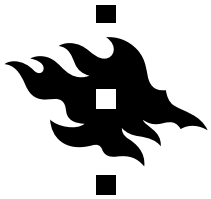
Submitted for consideration.

III **Björkqvist J, Pesonen A-K, Kuula L, Matinolli H-M, Lano A, Sipola-Leppänen M, Tikanmäki M, Wolke D, Järvelin M-R, Eriksson JG, Andersson S, Vääräsmäki M, Heinonen K, Räikkönen K, Hovi P, Kajantie E. 2018. Premature birth and circadian preference in young adulthood: evidence from two birth cohorts. Chronobiol Int. 35:555–564.**

"Taylor & Francis is pleased to offer reuses of its content for a thesis or dissertation free of charge contingent on resubmission of permission request if work is published." www.tandfonline.com/doi/full/10.1080/07420528.2017.1420078

IV **Björkqvist J, Hovi P, Pesonen A-K, Räikkönen K, Heinonen K, Järvenpää A-L, Eriksson JG, Andersson S, Kajantie E. 2018. Adults who were born preterm with a very low birth weight reported a similar health-related quality of life to their term-born peers. Acta Paediatr. 107:354–357.**

Permission granted in RightsLink, #4441221409538, John Wiley & Sons.



Doctoral Programme in Clinical Research,
Doctoral School in Health Sciences
Faculty of Medicine,
University of Helsinki, Finland

Children's Hospital and Pediatric Research Center
Helsinki University Hospital and
University of Helsinki, Finland

Finnish Institute for Health and Welfare,
Finland

Helsinki 2020

ISBN 978-951-51-5662-4